Archives of Internal Medicine

VOLUME 41 MAY, 1928 NUMBER 5

IODINE COMPOUNDS

THEIR SELECTIVE ABSORPTION BY THE HYPERPLASTIC THYROID GLAND OF THE DOG *

H. B. VAN DYKE, M.D.
CHICAGO

Marine and Feiss [1] and Marine and Rogoff [2] have demonstrated both by perfusion of the surviving isolated organ and by injections in vivo that the thyroid gland is able to remove iodide iodine from circulating fluids with extreme rapidity. Apparently no one, however, has studied iodine in other forms which are sometimes believed to behave characteristically when administered to persons suffering from disorders of the thyroid gland. The experiments reported in this paper have therefore been undertaken to learn, if possible, to what extent compounds containing iodine other than iodide iodine are selectively absorbed by the thyroid gland.

TECHNIC

In all of the experiments, the selective absorption of the various iodine compounds by the dog's hyperplastic thyroid gland was determined in vivo. When the preliminary experiments were performed about three years ago,[3] a large proportion of the animals had suitable goiters. In attempting to complete the work recently, I had great difficulty in finding goitrous dogs, probably because of the present extensive use of iodized salt which both dog and man ingest. Frequently, therefore, as in the experiment, the results of which are shown in table 4, a control piece of thyroid tissue was removed aceptically and its iodine concentration was determined before the experiment was performed. The difference in iodine concentration between the right and left lobes before the injection of an iodine compound was always much less than that which was considered significant in the experiments. Although most of the animals were under ether anesthesia during experimentation, similar results were obtained when narcosis was produced by barbital. If the glands were of sufficient size, control

* From the Department of Physiological Chemistry and Pharmacology, The University of Chicago.

1. Marine, David, and Feiss, H. O.: The Absorption of Potassium Iodid by Perfused Thyroid Glands and Some Factors Modifying It, J. Pharmacol. & Exper. Therap. **7**:577, 1915.

2. Marine, David, and Rogoff, J. M.: The Absorption of Potassium Iodid by the Thyroid Gland In Vivo, Following its Intravenous Injection in Constant Amounts, J. Pharmacol. & Exper. Therap. **8**:439, 1916.

3. van Dyke, H. B.: On the Absorption by the Hyperplastic Thyroid Gland of Various Forms of Iodine Introduced Intravenously, J. Pharmacol. & Exper. Therap. **25**:166, 1925.

samples were taken from the lowest part of each lobe. An iodine compound such as thyroxine was then injected intravenously. After a suitable time, a second sample consisting of the middle part of each lobe was removed. Thereupon potassium iodide solution was given intravenously; some minutes later, the remaining superior portions of the lobes were resected. The second and third samples were always incised before removal to make sure that the circulation, grossly judged by bleeding, was adequate.

In the preliminary experiments, iodide iodine appeared to be the most rapidly absorbed. Hence it was used as a means of comparing the absorption of the iodine of the particular compound being examined with that of the iodine of potassium iodide. The iodine determinations in thyroid tissue were made by Kendall's method.[4] In the case of inorganic iodine dissolved in isotonic saline solution, the determination was made by direct titration with standardized two-hundredth normal sodium thiosulphate solution. Often mention is made of specimens of thyroid which did not contain iodine; what is meant is that iodine could not be detected by Kendall's method. The tables illustrate typical results from twenty-six successful experiments.

THE SELECTIVE ABSORPTION OF IODINE IODINE

In seven experiments, small amounts of iodine dissolved in isotonic saline solution were administered intravenously, and the changes in the

TABLE 1.—*The Selective Absorption of Iodine Iodine and of Iodide Iodine*

		Ether anesthesia.	Mongrel of 7.0 Kg. weight	
Time, Minutes	Lobe	Weight of Dried Thyroid Gland Analyzed, Mg.	Iodine in Dried Thyroid Gland, per Cent	Comment
0	R	48.2	0	Control
5	..	.....	.....	10.0 mg. of iodine iodine in isotonic saline solution injected intravenously
20	L	95.5	0	
	L	120.9	0	
25	..	.....	.....	5.6 mg. of iodine as potassium iodide injected intravenously
30	R	71.2	0.007	Amounts too small to be titrated accurately
	R	84.2	0.012	

iodine concentration of the thyroid gland were determined. The experiment the results of which are given in table 1 is typical of what was found when the interval between injection and removal of samples was less than forty-five minutes. Iodine seemed not to be taken up by the gland. In some of the experiments in which the injection was made one to two hours before samples were resected, the iodine concentrations of the glands were definitely increased. However, the hyperplastic thyroid gland did not take up iodine iodine at the remarkably rapid rate at which it removes iodide iodine from the blood stream.

Probably free iodine is bound chiefly by the blood lipoids when it is injected intravenously. A certain amount may slowly be reduced to iodide iodine which is then removed from the circulating fluids by

4. Kendall, E. C.: Determination of Iodine in Connection with Studies in Thyroid Activity, J. Biol. Chem. **43**:149, 1920.

the thyroid. Free iodine in comparison with iodide iodine, even if one assumes that the former is absorbed, seems therefore to have little significance in thyroid physiology if experiments such as these are used as a criterion.

THE SELECTIVE ABSORPTION OF IODATE IODINE

Iodate iodine appeared to be taken up by hyperplastic glands much more quickly than iodine iodine. Ten experiments, including control observations, were performed because of the smaller difference between the selective absorption of iodate iodine and that of iodide iodine. Table 2 contains data from an experiment in which only iodate iodine

TABLE 2.—*The Selective Absorption of Iodate Iodine*

		Ether anesthesia.	Mongrel of 8.5 Kg. weight	
Time, Minutes	Lobe	Weight of Dried Thyroid Gland Analyzed, Mg.	Iodine in Dried Thyroid Gland, per Cent	Comment
0	L	130.1	0	
6	R	281.9	0	
7	..	.....	.....	9.95 mg. iodine as potassium iodate injected intravenously
18	L	264.6	0.036	
20.5	R	170.3	0.019	
32	L	180.1	0.038	
32	R	148.6	0.038	

TABLE 3.—*The Selective Absorption of Iodate Iodine and of Iodide Iodine*

		Ether anesthesia.	Mongrel of 10 Kg. weight	
Time, Minutes	Lobe	Weight of Dried Thyroid Gland Analyzed, Mg.	Iodine in Dried Thyroid Gland, per Cent	Comment
0	L	87.9	0.033	Control
7	R	179.4	0.032	
12	..	.....	.....	10.7 mg. iodine as potassium iodate injected intravenously
22	L	162.4	0.048	
24.5	R	218.4	0.053	
25	..	.....	.....	5.44 mg. iodine as potassium iodide injected intravenously
38	L	127.9	0.064	
38	R	179.7	0.072	

was administered. After about eleven or twelve minutes, there was a marked change in the iodine content of the gland. (The smaller value of the sample from the right lobe removed at 20.5 minutes probably was due to interference with the circulation by the ligation of the vessels of the lower pole on that side.) During the succeeding ten to fifteen minutes, there was little change in the amount of iodine contained in the thyroid.

An example of the second type of experiment is to be found in the experiment the data of which are given in table 3. Before injections, the iodine concentration of the gland was higher than in the first experiment. It is well known that the lower the initial concentration of

iodine in the thyroid, the greater is the ability of the gland to absorb selectively iodide iodine. In the second experiment, one would expect *a priori* less iodate and less iodide iodine to be taken up than in the experiment of table 2. There was a definite selective absorption of both iodate and iodide iodine. From other experiments and from those the data of which is presented, there appeared to be a greater increase in the final concentration of iodine after the injection of iodide than one would encounter if iodate instead of iodide iodine had been given on the second occasion. It should be noted that only about half as much iodide iodine was usually administered.

Some idea of the rate at which iodide iodine was taken up by such a hyperplastic gland may be gained from an examination of table 4, in the experiment of which thyroxine iodine was first injected. Usually ten minutes after the administration of about 5 mg. of iodide iodine into a suitable animal, there was an increase in the concentration of iodine in the thyroid gland equal to that following the administration of twice as much iodate iodine at a somewhat longer period previously.

THE SELECTIVE ABSORPTION OF THYROXINE IODINE

As is generally known, the administration of thyroxine to an animal characteristically increases the basal metabolic rate after a prolonged latent period. Just how this occurs is not known; but it seemed possible that some light might be thrown on the mechanism of the action of thyroxine by ascertaining whether or not the hormone, so far as it can be identified by its iodine, is acutely taken up by the hyperplastic thyroid gland which selectively absorbs iodate and especially iodide iodine. Thyroxine made by Kendall's method [5] and by the later process of Harington [6] was used in four experiments, all of which gave identical results. From one to two hours after the injection of thyroxine, it was possible to detect only untitratable traces of iodine in the samples of thyroid analyzed. However, there was a well marked acute increase in iodine concentration in samples of thyroid removed from the same animal a much shorter time after the injection of a considerably smaller amount of iodide iodine. These results are illustrated in the data of table 4. The thyroxine used in this experiment had been made by Harington's method.

Whether or not such observations have any significance as to the pharmacologic action of thyroxine remains unsettled. Too little time elapsed between injection of the thyroxine and analysis of the thyroid for the characteristic effect on metabolism to have appeared.

5. Kendall, E. C.: Isolation of the Iodine Compound Which Occurs in the Thyroid, J. Biol. Chem. **39**:125, 1919. Purchased from E. R. Squibb and Sons Company.

6. Harington, C. R.: Isolation of Thyroxine from the Thyroid Gland, Biochem. J. **20**:293, 1926. Purchased from The British Drug Houses, Ltd.

THE SELECTIVE ABSORPTION OF IODINE COMPOUNDS AFTER BILATERAL LIGATION OF THE SUPRARENAL GLANDS

Some years ago, Marine and Baumann [7] reported that there appeared to be a definite relationship between the thyroid gland and the suprarenal cortex in the maintenance of the normal metabolism of the rabbit. Resection of the main suprarenal bodies usually resulted in an increased production of heat which failed to appear if the animals had previously been thyroidectomized. Marine and Baumann were of the opinion that in the rabbit there was little interference with the storage of iodine of the thyroid glands of animals that had been subjected to bilateral suprarenalectomy alone. At about the same time, Black, Hupper and Rogers [8] published data from which they concluded that the feeding of suprarenal

TABLE 4.—*The Selective Absorption of Thyroxine Iodine and of Iodide Iodine*

Ether anesthesia. Young fox terrier mongrel of 8.0 Kg. weight

Time			Weight of Dried Thyroid Gland Analyzed,	Iodine in Dried Thyroid Gland,	
Hr.	Min.	Lobe	Mg.	per Cent	Comment
..	..	R	153.9	0	Sample removed aseptically day preceding experiment
0	..	L	44.0	0	Additional control
0	3	..	.....	.....	13.2 mg. of iodine as thyroxine (20.25 mg.) dissolved in 4.5 cc. of tenth normal sodium hydroxide injected intravenously
1	31	R	122.9	Trace	
1	38	L	69.0	Faint trace	
1	38	L	147.9	Trace	
1	39	..	.....	.....	4.88 mg. of iodine as potassium iodide injected intravenously
2	5	L	149.1	0.047	
		L	145.6	0.062	
		R	213.5	0.047	

"residue" to dogs was accompanied by an increase in content of iodine of the thyroid. There thus was a possibility of this interrelationships being further manifested by an alteration in the ability of the hyperplastic thyroid gland of the dog to take up iodine after resection of the suprarenal glands.

In five successful experiments, the suprarenal glands were either removed or ligated. The completeness of the operation was confirmed

7. Marine, David, and Baumann, Emil J.: Influence of Glands with Internal Secretions on the Respiratory Exchange: III. Effect of Suprarenal Insufficiency (by Removal) in Thyroidectomized Rabbits, Am. J. Physiol. **59**:353 (Feb.) 1922; V. Effect of Suprarenal Insufficiency (by Removal) in Thyroidectomized Rabbits, J. Metab. Research **1**:777 (June) 1922; VI. Further Data on the Effect of Suprarenal Insufficiency (by Removal) in Rabbits, J. Metab. Research **2**:1 (July) 1922.

8. Black, E. M.; Hupper, Marjorie, and Rogers, John: The Effects of Adrenal Feeding on the Iodin Content of the Thyroid Gland, Am. J. Physiol. **59**:222 (Feb.) 1922.

by necropsy in each case. After from six to seven hours, further thyroid samples were removed and an iodine compound was injected intravenously immediately afterward. Analysis of the final samples revealed to what extent iodine was selectively bound by the thyroid gland under such conditions.

The experiment of table 5 indicates more clearly how the data were obtained. After suprarenal resection, as far as the thyroid gland was concerned, there did not seem to be any change in either the iodine content or in the ability of the gland selectively to absorb iodide iodine. In other experiments, iodine and iodate iodines were taken up by hyperplastic thyroid glands exactly as in normal animals. It is obvious, of course, that the results might have been different had I injected the iodine compounds at a considerably later period when symptoms of insufficiency of cortical "secretion" would have been manifest.

TABLE 5.—*The Selective Absorption of Iodide Iodine after Bilateral Ligation of the Adrenal Glands*

Ether anesthesia. Mongrel of 10 Kg. weight

Time			Weight of Dried Thyroid Gland Analyzed,	Iodine in Dried Thyroid Gland,	
Hr.	Min.	Lobe	Mg.	per Cent	Comment
0	18	..	.....	.....	Right suprarenal gland ligated
0	32	..	.....	.....	Left suprarenal gland ligated
0	57	L	440.8	0.022	Control
		L	313.4	0.026	
		L	466.6	0.020	
6	36	L	472.5	0.021	
		L	344.6	0.021	
6	45	..	.....	.....	15.3 mg. iodine as potassium iodide injected intravenously
7	5	R	414.0	0.056	
		R	322.2	0.052	

COMMENT

The results of most of the experiments which have been performed in an attempt to determine the manner in which iodine is removed from the gastro-intestinal tract have led to the conclusion that if iodine iodine is administered, it is found to have been reduced to iodide in serum.[9] Moreover, Marine and Rogoff [10] pointed out that eight hours after the injection of an iodide solution into an animal having a well marked hyperplasia of the thyroid gland, pharmacologic evidences of an altered secretion appeared. These facts, together with the results of the experiments cited in this paper, suggest that in practice iodide iodine is of chief

9. Sollmann, Torald: The Fate of Iodin, Iodids, and Iodates in the Body, J. Pharmacol. & Exper. Therap. **9**:269, 1917.

10. Marine, David, and Rogoff, J. M.: How Rapidly Does the Intact Thyroid Gland Elaborate its Specific Iodin Containing Hormone? J. Pharmacol. & Exper. Therap. **9**:1, 1916.

pharmacologic significance in altering thyroid secretion. There appears to be little experimental basis for the use of free iodine, even if loosely linked with iodides, as in Lugol's solution, in the treatment of patients with various types of goiter.

As far as the experiments reported in this paper are concerned, the reason for the slight absorption of iodine iodine and especially of thyroxine iodine perhaps is that these substances were more or less selectively taken up by other tissues in the body. Some idea of the correctness of such a view could be furnished by estimations of the iodine content of the blood coincidently with the removal of samples of thyroid and of other organs.

SUMMARY

1. An attempt has been made by acute experiments to determine quantitatively the rates at which the hyperplastic thyroid gland of the dog selectively absorbs various iodine compounds. Thyroxine iodine is very slowly taken up, while free iodine is absorbed relatively more rapidly. Iodate iodine is bound quickly by such glands but apparently not so quickly as iodide iodine, which is selectively absorbed by the hyperplastic gland more rapidly than any of the iodine compounds studied.

2. The selective absorption of iodine, iodate and iodide iodines is unaffected by complete bilateral ligation of the suprarenal glands six or seven hours previously.

THE EFFECTS OF DRUGS ON CARDIAC OUTPUT

VI. THE EFFECT OF EPHEDRINE ON THE MINUTE CARDIAC OUTPUT OF NORMAL DOGS *

CHARLES P. WILSON, M.D.

COBB PILCHER, M.D.

AND

T. R. HARRISON, M.D.

NASHVILLE, TENN.

INTRODUCTION

The number of drugs which have been shown to be cardiac stimulants is not large and the result of their use in combating acute circulatory insufficiency has not been encouraging. The action of three drugs commonly used for this purpose, caffeine, camphor and strychnine, has been studied by us on normal dogs,[1] and Blalock [2] has studied the effect of caffeine and ether on the minute cardiac output of dogs in hemorrhagic shock. Caffeine decreased the cardiac output of normal dogs and slightly increased the output in mild shock; camphor had no effect, and strychnine caused a consistent increase when given to normal dogs. Ether, in mild shock, caused an increase in the output but in severe shock was found to decrease the output. The action of epinephrine hydrochloride is well known by virtue of the work of many investigators; Pilcher, Wilson and Harrison [3] have recently shown that following the administration of this drug to normal dogs there is an immediate, temporary increase in the circulatory minute volume.

Chen and his co-workers have studied the action of ephedrine from many angles, and by means of the blood pressure, pulse rate and myocardiograph have concluded that it increases the output of the heart,[4] having an action like that of epinephrine hydrochloride in this respect, except that the increase after ephedrine is of longer duration. This point is important, warranting further study and confirmation in the intact animal. The purpose of the present paper is to report such a study.

METHODS

The hydrochloride of ephedrine was used, and since the pharmacology has been fully worked out by Chen, only doses comparable to human therapeutic doses were studied. For intravenous administration 0.5 and 1 mg. per kilogram were

* From the Department of Medicine, Vanderbilt University.

1. Wilson, C. P.; Pilcher, C., and Harrison, T. R.: Am. Heart J. **2**:618, 1927. Pilcher, C.; Wilson, C. P., and Harrison, T. R.: Action of Drugs on Cardiac Output; Effect of Camphor and Strychnine on Cardiac Output of Intact Unnarcotized Dogs, Arch. Int. Med. **40**:605 (Nov.) 1927.

2. Blalock, A.: Mechanism and Treatment of Experimental Shock; Shock Following Hemorrhage, Arch. Surg. **15**:762 (Nov.) 1927.

3. Pilcher, C.; Harrison, T. R., and Wilson, C. P.: Am. Heart J. **2**:630, 1927.

4. Chen, K. K., and Meek, J. W.: J. Pharmacol. & Exper. Therap. **28**:31, 1926.

given; for subcutaneous administration 1 and 2 mg. per kilogram, and for oral administration 3 mg. per kilogram.

In one experiment 4 mg. per kilogram was given intravenously, and after two determinations death occurred. Intravenous injections were made into the external jugular vein and "oral" administration was accomplished by means of a stomach tube.

In all, eighteen experiments were performed on nine dogs. The intravenous method was studied six times, the subcutaneous method nine times and the oral method three times. In one experiment the dog probably developed a small hemopericardium insufficient to be fatal, and the results of the experiment were discarded.

The dogs weighed from 7 to 20 Kg., and they had been previously trained to the method so that they were quiet as long as the effect of the drug was not evident.

The minute cardiac output was determined by the Fick principle; the technic employed is fully described by Harrison and Leonard.[5]

The determinations were made at certain time intervals in order to find roughly the rapidity with which the action developed, and the duration of this action.

In a number of experiments blood samples were drawn while the oxygen consumption was being determined. This procedure has been found repeatedly not to cause any change in the minute cardiac output and, obviously, has distinct advantages.

RESULTS

General.—Following the intravenous and subcutaneous injection of ephedrine, and to a less extent the oral administration, all of the dogs became more restless and more easily excitable, and there was a marked dilatation of the pupils. No deleterious effect was noted either during or after experimentation, except in the first experiment, and in this there was a series of events worthy of detail. A dose of 4 mg. per kilogram was given intravenously over a period of six minutes to a dog weighing 14.8 Kg. An immediate slowing of the pulse was noted (as will be seen later), and the pupils became dilated. Ten minutes after the injection the eyes appeared to be more prominent, and within twenty minutes there was respiratory embarrassment and coincident cyanosis of the buccal mucous membranes. The respirations became jerky and gasping, and there was retching without vomiting, ballooning of the chest and slight frothing at the mouth. The animal appeared spastic, frank exophthalmos developed and the pulse rate became still slower. It was taken off the table, its gait was staggering and spastic and the retching and frothing continued. After wandering aimlessly for several minutes the animal fell over without convulsions. The pulse was obtained for two minutes after the respirations ceased, and artificial respiration did not have any effect. No apparent cause of death was found at autopsy.

Pulse.—The pulse rate was counted frequently throughout the experiments, and in spite of the variability in the pulse rate in dogs, there were noteworthy changes.

5. Harrison, T. R., and Leonard, B. W.: J. Clin. Investigation **3**:1, 1926.

Following intravenous administration there was a decrease from the lowest control pulse rate, within the first five minutes, of from 8 to 42 per cent or an average decrease of 24 per cent. This was generally followed by an increase, the average in this group being an increase of 24 per cent, while subsequent pulse rates varied usually only slightly from the control rate.

Fifteen minutes after the subcutaneous injection there was a decrease in the pulse rate of 13 per cent with limits from + 9 to — 39 per cent. Later, the average pulse rate was near the control rate although still below at the end of thirty and sixty minutes, and above at the end of two hours.

No appreciable change took place in the pulse rate in those experiments in which ephedrine was given orally.

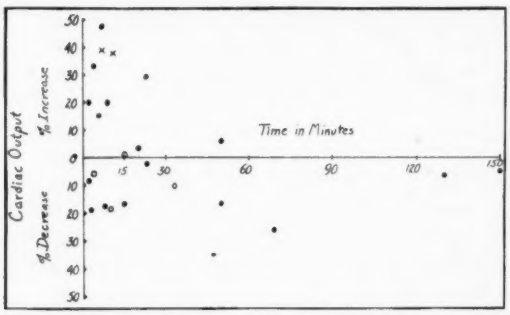

Chart 1.—The effect of ephedrine on the minute cardiac output of normal dogs at various time intervals after intravenous injection; circle indicates 0.5 mg. per kilogram; black dot, 1 mg. per kilogram; *x*, 4 mg. per kilogram.

Blood Gases.—When the animals were breathing oxygen, blood samples naturally showed an increase in the arterial oxygen content. The experiments in which the blood samples were drawn immediately before or from three to five minutes after the oxygen consumption was determined, showed in each case after the administration of ephedrine an increase in the arterial oxygen content from 1 to 2.5 volumes per cent. This change was not evident during the final determinations when the blood flow approached the control level. The changes in the venous oxygen content generally led to a diminution of the arteriovenous difference.

Oxygen Consumption.—An increase in the oxygen consumption lasting from fifteen to thirty minutes was noted in every experiment following intravenous injection. The degree of increase varied considerably in individual experiments. After the subcutaneous administration the oxygen consumption increased more than 10 per cent in five

TABLE 1.—*The Effect of Ephedrine Intravenously on the Pulse Rate, Oxygen Consumption and Minute Cardiac Output*

		Before Ephedrine				After Ephedrine				Percentage Change	
Experiment	Weight Kg.	Pulse Rate per Minute	Oxygen Consumption per Minute Cc.	Cardiac Output per Minute Cc.	Dose Mg. per Kg.	Time After Administration, Minutes	Pulse Rate per Minute	Oxygen Consumption per Minute Cc.	Cardiac Output per Minute Cc.	Oxygen Consumption	Cardiac Output
E3	11.3	88	97.1	2,000	0.5	4	76	151.7	1,890	+55	−5.5
	....	...	.....	.....	...	10	192	118.4	1,630	+21.4	−18.5
	....	...	.....	.....	...	15	90	99.9	2,010	+2.2	+0.5
V56	....	...	.....	.....	...	33	116	99.9	1,800	+2.2	−10
E2	13.6	114	107.8	1,645	1	2	66	154.4	1,500	+43	−8.8
	....	...	.....	.....	...	6	64	122.8	1,900	+14	+15.5
	....	...	.....	.....	...	23	112	119.0	2,130	+10.3	+29.5
V74	....	...	.....	.....	...	130	100	107.3	1,500	−0.6	−5.2
E4	8	100	69.9	1,840	1	4	92	92.0	2,450	+31.5	+33.1
	....	...	.....	.....	...	7	162	92.0	2,720	+31.5	+47.8
	....	...	.....	.....	...	22	72	99.4	1,910	+42.0	+3.8
V21	....	...	.....	.....	...	50	64	73.6	1,540	+5.0	−16.2
	....	...	.....	.....	...	150	148	70.8	1,750	+1.2	−5.0
E5	14	70	98.9	2,485	1	3	60	123.3	2,020	+34.5	−18.7
	....	...	.....	.....	...	9	84	147.2	2,980	+49.0	+20.0
	....	...	.....	.....	...	23	80	161.9	2,480	+63.5	−1.0
V53	....	...	.....	.....	...	50	72	139.8	2,680	+41.0	+6.3
E6	12	92	114.7	2,500	1	2	64	131.0	3,010	+14.0	+20.5
	....	...	.....	.....	...	8	96	182.0	2,060	+58.8	−17.6
	....	...	.....	.....	...	15	96	136.5	2,000	+19.0	−16.4
	....	...	.....	.....	...	47	132	118.3	1,640	+3.2	−34.4
V58	....	...	.....	.....	...	69	108	106.5	1,850	−7.2	−26.0
	....	...	.....	.....	...	20 hrs.	140	87.7	1,870	−23.5	−25.2
E1	14.8	120	143.2	2,070	4	7	88	150.1	2,840	+4.8	+37.2
	....	...	.....	.....	...	11	112	161	2,855	+12.4	+38
V71	....	...	.....	.....	...	...	...	.....	.....	.....	.....

experiments in the first fifteen minutes, while in one there was only a slight change from the control. Of these increases of more than 10 per cent, one lasted thirty minutes and another was still over 10 per cent at the end of two hours. In those experiments in which a stomach tube was passed, there was a decrease in the consumption of oxygen within fifteen minutes in two dogs and a slight increase in one, while subsequent determinations proved to be variable.

Cardiac Output.—1. Ephedrine Given Intravenously: Immediately following the injection there was a decrease in the minute cardiac output in three experiments averaging 11 per cent, while in the other three experiments there was an average increase of 26.9 per cent. After thirty minutes the output had returned to normal limits. Chart 1 shows the results of all the intravenous experiments. One dog (V_{56} E_3, see also E_6) reacted to the injection with a pronounced decrease in the minute

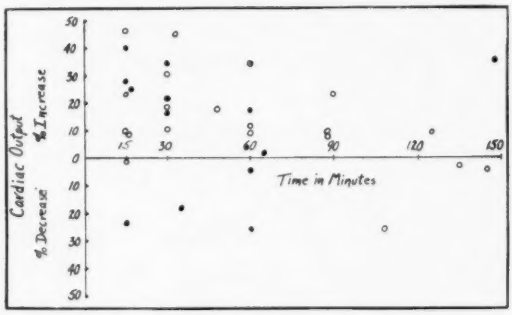

Chart 2.—The effect of ephedrine on the minute cardiac output of normal dogs at various time intervals after subcutaneous injection; black dot indicates 1 mg. per kilogram; circle, 2 mg. per kilogram.

output, and a half hour later still had not returned to the normal control level. This dog was also used in studying epinephrine hydrochloride and was found to react with a decrease in the minute cardiac output. The question of idiosyncrasy to these drugs suggests itself as an explanation.

2. Ephedrine Given Subcutaneously: Regardless of the dose, in five experiments there was an average increase in the minute output of 32.6 per cent within fifteen minutes, while in one there was a decrease of 23.5 per cent and in three the result was within the limit of error allowed, — 10 per cent (chart 2). After thirty minutes there was an average increase of 25.3 per cent in seven determinations and a decrease of 18 per cent in one. There was a return to normal in five experiments at the end of sixty minutes; in two the time required was from 120 to 145 minutes, and in two others the return to a normal flow was not studied.

TABLE 2.—*The Effect of Ephedrine Subcutaneously on the Pulse Rate, Oxygen Consumption and Minute Cardiac Output*

		Before Ephedrine				After Ephedrine				Percentage Change	
Experiment	Weight Kg.	Pulse Rate per Minute	Oxygen Consumption per Minute Cc.	Cardiac Output per Minute Cc.	Dose Mg. per Kg.	Time After Administration, Minutes	Pulse Rate per Minute	Oxygen Consumption per Minute Cc.	Cardiac Output per Minute Cc.	Oxygen Consumption	Cardiac Output
E7	14.5	88	140.6	2,580	1	15	96	157.2	3,310	+11.7	+28.3
	....	...	.....	.....	...	30	88	144.3	3,000	+2.6	+16.3
V53	....	...	.....	.....	...	60	96	140.6	2,470	0	−4.2
E8	8.6	120	99.9	2,660	1	15	100	94.4	2,110	−5.4	−23.5
	....	...	.....	.....	...	30	84	94.4	3,240	−5.4	+21.7
V31	....	...	.....	.....	...	60	...	92.5	1,970	−7.2	−26.0
E9	10.5	112	89.2	2,500	1	17	80	81.0	3,120	−9.0	+24.8
	....	...	.....	.....	...	35	88	92.9	2,050	+4.0	−18.0
V70	....	...	.....	.....	...	65	100	95.7	2,540	+7.2	+1.6
E10	9.3	72	79.1	2,310	1	15	60	108.6	3,240	+37.0	+40.2
	....	...	.....	.....	...	30	64	97.5	3,110	+23.0	+34.6
V73	....	...	.....	.....	...	60	64	72.5	2,710	−8.2	+17.3
E11	16	60	117.1	2,300	2	15	64	146.4	3,370	+25.0	+46.5
	....	...	.....	.....	...	30	64	153.7	2,720	+31.2	+18.2
V78	....	...	.....	.....	...	60	66	139.1	3,090	+18.8	+34.4
	....	...	.....	.....	...	90	72	132.7	2,830	+13.3	+23.0
	....	...	.....	.....	...	145	84	129.0	2,200	+10.1	−4.4
E12	20	96	144.0	4,800	2	16	72	162.0	5,190	+12.5	+8.3
	....	...	.....	.....	...	48	76	176.5	5,650	+22.5	+17.9
V77	....	...	.....	.....	...	88	64	142.2	5,160*	−1.1	+7.5
	....	...	.....	.....	...	108	88	162.0	3,550	+12.5	−26.0
E13	13.2	66	94.9	2,220	2	15	72	99.0	2,240	+4.2	+9.0
	....	...	.....	.....	...	33	78	104.4	3,220	+10.0	+45.0
V53	....	...	.....	.....	...	60	72	86.4	2,480	−8.8	+11.6
	....	...	.....	.....	...	88	72	100.8	2,400	+6.0	+8.1
	....	...	.....	.....	...	148	68	100.8	3,000	+6.0	+35.1
	....	...	.....	.....	...	208	64	99.0	2,010	+4.2	−9.4
E14	7.7	85	70.2	2,010	2	15	76	77.4	2,480	+10.0	+23.3
	....	...	.....	.....	...	30	124	75.6	2,630	+7.8	+30.8
V21	....	...	.....	.....	...	125	100	68.4	2,190	−2.5	+9.0
E15	10.7	92	90.7	2,480	2	15	60	102.3	2,440	+13.0	−1.6
	....	...	.....	.....	...	30	80	98.6	2,740	+8.9	+10.5
V70	....	...	.....	.....	...	60	80	100.4	2,700	+10.2	+8.9
	....	...	.....	.....	...	135	84	93.0	2,400†	+2.5	−3.2

* Arterial oxygen content assumed to be the same as in preceding determination.
† Blood samples did not check average taken for calculation.

3. Ephedrine Given Orally: Fifteen minutes after administration there was an increase in the circulatory minute volume of 18.3 per cent in one experiment and no change in another (chart 3). Three determinations made at the end of thirty minutes showed an average increase of 20 per cent in the output of the heart. In 120 minutes the cardiac output had returned to normal. As there are only three experiments in this group conclusions drawn from them must be guarded. Although the change in the minute output was greater in two experiments than it was in any by the intravenous or subcutaneous method and the average of the three oral experiments stands well above the other averages, we only wish this to be considered as a suggestive observation.

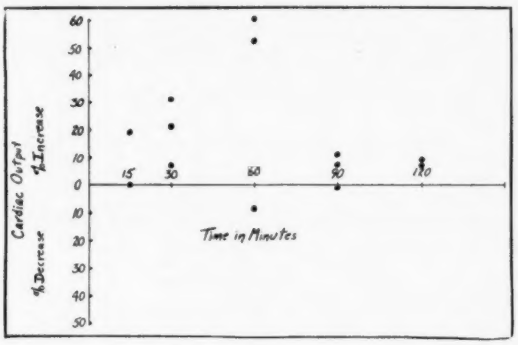

Chart 3.—The effect of ephedrine on the minute cardiac output of dogs at various time intervals after oral administration.

COMMENT

From the foregoing data it is evident that the minute cardiac output of normal dogs generally increases in response to ephedrine given intravenously, subcutaneously or by mouth in therapeutic doses. In a comparison of charts 1, 2 and 3, it is noted that the increase in cardiac output develops most rapidly following the intravenous administration of ephedrine; second most rapidly after the subcutaneous injection, and least rapidly when the drug is given orally. This, of course, is to be expected. The duration of the action is about equal for the subcutaneous and oral method of administration. Chart 4 is made by averaging the results of all experiments and plotting the results against time intervals. While the number of experiments does not allow such mean values to be an exact representation of the effect of the drug it does give a rough indication of the degree and duration of action.

The problem of clinical importance is concerned with the use of ephedrine in acute circulatory insufficiency, commonly called shock. A

TABLE 3.—*The Effect of Ephedrine Orally on the Pulse Rate, Oxygen Consumption and Minute Cardiac Output*

Experiment	Weight Kg	Before Ephedrine: Pulse Rate per Minute	Before Ephedrine: Oxygen Consumption per Minute Cc.	Before Ephedrine: Cardiac Output per Minute Cc.	Dose Mg. per Kg.	Time After Administration, Minutes	After Ephedrine: Pulse Rate per Minute	After Ephedrine: Oxygen Consumption per Minute Cc.	After Ephedrine: Cardiac Output per Minute Cc.	Percentage Change: Oxygen Consumption	Percentage Change: Cardiac Output
E19	13	80	121.3	2,470	3	30	72	101.2	3,240	−16.3	+31.2
	....	...	.....	.....	...	60	70	104.2	3,970	−14.2	+60.7
V53	....	...	.....	.....	...	90	68	107.6	2,890	−11.4	+11.0
	....	...	.....	.....	...	120	60	103.6	2,700	−14.6	+9.3
E18	8.9	80	101.8	2,095	3	15	60	87.8	2,500	−12.2	+19.3
	....	...	.....	.....	...	30	78	95.2	2,250	−4.8	+7.4
	....	...	.....	.....	...	60	60	124.4	3,020	+22.1	+52.8
V73	....	...	.....	.....	...	90	60	93.3	2,290	−8.4	+7.5
	....	...	.....	.....	...	120	56	102.5	2,240	+0.7	+7.3
E19	11	104	97.0	2,890	3	15	104	100.6	2,890	+3.6	0
	....	...	.....	.....	...	30	100	117.1	3,510	+20.8	+21.4
V70	. ..	...	.....	.....	...	60	96	97.0	2,650	0	−8.3
	....	...	.....	.....	...	90	92	104.3	2,870	+7.6	−0.7

drug, to be of most use in combating this emergency, must fulfill certain requirements; namely, it must increase the circulatory minute volume an appreciable amount and maintain this increase for an appreciable length of time without any depressing after effects; cause a maintained increase of the blood pressure, and decrease the pulse rate.

Chen [6] has reported good results following the use of ephedrine in experimental shock, satisfying the preceding requirements, provided the degree of shock is not too severe. He believes, as do we, that the results are accomplished by direct action on the heart muscle. Blalock [2] has arrived at the same conclusions in mild hemorrhagic shock, with the exception of the slowing of the pulse rate. In severe shock, ephedrine, according to Blalock, has less beneficial effects and may be injurious. The effect of ephedrine on the pulse rate in anesthetized dogs was not studied by us, but Chen has shown that in this state there is an acceleration in the rate.

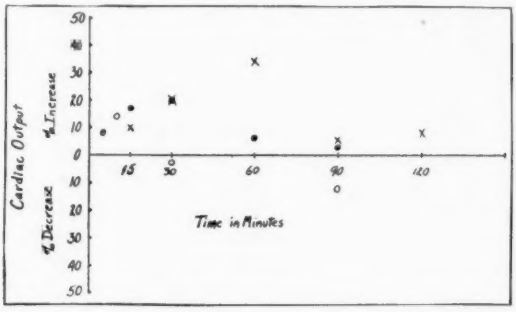

Chart 4.—The average change in minute cardiac output at various time intervals after the administration of ephedrine by three different methods—intravenous, subcutaneous and oral; circle indicates intravenous; black dot, subcutaneous, *x*, oral.

We encountered but one instance in this series which would lead us to say that ephedrine was a dangerous drug, and in this experiment we were using a far smaller amount than that given by Chen [7] as the minimal lethal dose for dogs intravenously, which is from 70 to 75 mg. per kilogram. We did not follow this observation with more experiments and the doses used in other instances did not lead us to believe that there was any great danger in the administration of ephedrine in small amounts.

Chen and Meek [4] have shown that ephedrine diminishes the size of the spleen. Such an action would afford an explanation of the increase in the oxygen content of the arterial blood, in as much as it would cause

6. Chen, K. K.: J. Pharmacol. & Exper. Therap. **26**:83, 1925.
7. Chen, K. K.: J. Pharmacol. & Exper. Therap. **27**:61, 1926.

an increase in the number of circulating red blood corpuscles and, therefore, in the oxygen carrying capacity of the blood. That this is a function of the spleen has been maintained by Barcroft for a number of years. Lamson [8] is not in accord with this idea, having concluded from a number of experiments concerned with the effect of epinephrine hydrochloride on the red blood count that the liver, or the portal circulation, is the seat of the series of events which leads to the temporary polycythemia.

It would seem, from an examination of the tables, that the increases in the oxygen consumption had a decided bearing on the values obtained for the cardiac output. The fact that this does not always occur is important, and also that we had a large number of experiments in which the oxygen consumption varied considerably during the control periods but the arteriovenous oxygen difference compensated in these, giving determinations on the circulatory minute volume which were in agreement.

Our results using epinephrine hydrochloride are reported in a preceding paper. In a comparison of the dosage used and the consistency and duration of action of epinephrine hydrochloride and ephedrine the following points are noted. The dose of epinephrine hydrochloride used corresponds to a large therapeutic dose for an adult patient, while the amount of ephedrine given is probably the average amount that would be given to a patient. Intravenously, epinephrine hydrochloride increases the circulatory minute volume more consistently than ephedrine, whereas the duration of action is about one third as long, the ratio being five minutes for epinephrine hydrochloride to fifteen minutes for ephedrine. Subcutaneously, ephedrine and epinephrine hydrochloride in the doses used have practically the same effect on the cardiac output, as regards consistency, degree and duration of action. Ephedrine usually causes a slowing of the pulse rate of normal dogs, while epinephrine hydrochloride usually has the opposite effect.

Because of this and because the action of ephedrine is less variable, and furthermore because secondary depression following the initial increase in cardiac output occurs more frequently when epinephrine hydrochloride is used, we believe that ephedrine is the better drug of the two in the treatment of circulatory collapse.

SUMMARY

Ephedrine given intravenously to normal dogs usually causes an immediate increase in the minute cardiac output, which lasts fifteen minutes or longer. If the drug is given subcutaneously the action is more uniform and of a greater degree, developing within fifteen minutes and

8. Lamson, P. D.: J. Pharmacol. & Exper. Therap. **9**:129, 1916.

lasting forty-five minutes or longer. If it is given orally an increase develops after thirty minutes and lasts about an hour.

In normal dogs the pulse rate is slowed after the intravenous and subcutaneous administration of ephedrine.

The subcutaneous method of administration of ephedrine for its effect on the circulatory mechanism is probably the most suitable, although the oral method gave the highest average in the few experiments performed.

CONCLUSIONS

Ephedrine increases the minute cardiac output, and the results of its use in shock indicate that it is of value as a cardiac stimulant.

DUODENAL ULCER

OBSERVATIONS ON THE BEHAVIOR OF STOMACH AND DUODENUM IN THE PRESENCE OF PAIN *

MALCOLM J. WILSON, M.D.
TORONTO

Various hypotheses have been advanced in explanation of the pain in duodenal ulcer. This pain has been ascribed to irritation of exposed nerve endings in the ulcer base by the acid gastric juice, or to sensitization of the pain-producing mechanism in some way by acid. Bonninger,[1] Palmer [2] and others hold such views. Mechanical irritation by coarse particles of food is the cause assigned by Pick.[3] Spasm of the pyloric sphincter or of the duodenal cap has been put forward by Glaessner and Kreuzfuchs [4] and many others. Tension, due to an inhibition of relaxation of the pyloric sphincter, combined with strong gastric peristalsis, has been advanced by Hurst [5] as the cause. That distention of the stomach is an important element in the pain of gastric ulcer and that this pain is readily relieved by passing a tube into the stomach is stated by Poulton.[6] That the pain is possibly due to movement of the pylorus toward the midline, "thus putting traction on the duodenum," has been suggested by Alexis Thomson.[7] Again, it is conceivable that the pain might result from an exaggeration of the normal hunger contractions, and indeed, the term "hunger pains" is frequently employed in this connection by both patients and physicians.[8] Finally, it is possible that spasm elsewhere than at the pyloric sphincter can cause pain, as in a case described by Reynolds and McClure.[9]

---

* Thesis submitted for Degree of Doctor of Medicine, University of Toronto. The results of this investigation were presented at the meeting of the American Gastro-Enterological Association, Atlantic City, N. J., May 2, 1927.

* From the Department of Medicine, University of Toronto, and the Medical Service of the Toronto General Hospital.

1. Bonninger, M.: Berl. klin. Wchnschr. **45**:396, 1908.
2. Palmer, W. L.: Mechanism of Pain in Gastric and Duodenal Ulcer, Arch. Int. Med. **39**:109 (Jan.) 1927.
3. Pick, A.: Wien. klin. Rundschau **20**:1, 1906; Wien klin. Wchnschr. **63**: 105, 1913.
4. Glaessner, K., and Kreuzfuchs, S.: München. med. Wchnschr. **60**:582, 1913.
5. Hurst, A. F.: The Sensibility of the Alimentary Canal, London, 1911, p. 55.
6. Poulton, E. P.: Lancet **200**:263, 1921.
7. Thomson, A.: Brit. M. J. **1**:648, 1909.
8. Thomson (footnote 7). Moynihan, B. G. A.: Duodenal Ulcer, London, 1910, p. 118; Lancet **182**:9, 1912.
9. Reynolds, L., and McClure, C. W.: Motor Phenomena Occurring in Normal Stomachs, Arch. Int. Med. **29**:1 (Jan.) 1922.

When one examines these hypotheses a little more closely, one finds that Bonninger diagnosed gastric ulcer by putting 100 or 200 cc. of tenth normal hydrochloric acid into the empty stomach through a tube. Only patients with ulcer experienced pain, and the healing of the ulcer could be gaged by the lessening of the response to this test. On the other hand, Hurst introduced 0.5 per cent hydrochloric acid into the stomachs of six patients with gastric ulcer, and no sensation whatever was produced. He concluded that "contact with free hydrochloric acid is not the direct cause of the pain in gastric and duodenal ulcer." Ryle [10] reported instances of patients with gastric ulcer who had complete achlorhydria with severe and characteristic pain, and similar instances of duodenal ulcer associated with hypochlorhydria have been described by Moynihan,[11] Hardt [12] and others. Recently, however, Palmer reported that the administration of from 200 to 400 cc. of 0.5 per cent hydrochloric acid caused pain in several patients with duodenal ulcer and in several with gastric ulcer. He stated that "hydrochloric acid is the normal stimulus to the pain producing mechanism of sensitive peptic ulcers." Pick's suggestion that mechanical irritation of food is the cause of the pain fails to explain the relief obtained when more food is taken or when sodium bicarbonate is ingested. Further, the pain does not occur until most of the meal has passed the site of the ulcer. In 1892, Ewald [13] suggested that "the surface of the ulcer is distorted and its nerves irritated by the contractions accompanying digestion." In 1913, Glaessner and Kreuzfuchs [4] found that the pain of duodenal ulcer was due to prolonged "late" pyloric spasm, as evidenced by a persistent clear interval between the gastric and duodenal shadows on roentgen-ray examination. Reynolds and McClure [9] found that spasm of the pyloric sphincter, as shown by the absence of barium in the cap and duodenum during strong gastric peristalsis, was present in a number of persons with duodenal ulcer during the time of pain. In one patient, however, severe pain was felt while barium was seen to be passing through the sphincter; the next peristaltic wave showed complete pylorospasm, although the pain had ceased. Ginsburg and his associates [14] showed that pain was felt at or after the maximum of hunger contraction, and this was confirmed by Carlson,[15] Hardt [12] and others. This hypothesis failed

10. Ryle, J. A.: Gastric Function in Health and Disease, New York, Oxford University Press, 1926, p. 118.

11. Moynihan (footnote 8, second reference).

12. Hardt, L. L. J.: Gastric Pain, J. A. M. A. **70**:837 (March 23) 1918.

13. Ewald, C. A.: Diseases of the Stomach, New York, 1892, p. 244.

14. Ginsburg, H.; Tumpowsky, I., and Hamburger, W. W.: Pain in Gastric Ulcer, J. A. M. A. **67**:990 (Sept. 30) 1916.

15. Carlson, A. J.: Am. J. Physiol. **45**:80, 1917.

to explain why patients seldom had pain before breakfast and why in many cases it passed off before the next meal. Further, Homans [16] found that pain may occur independently of muscular activity of the stomach, as judged by changes in the pressure of a balloon in the stomach. Also, Ortmayer [17] showed that no change occurred in the character of the gastric contractions during the relief of pain by alkalis.

That spasm of a part of the stomach may be the cause of pain in some persons with duodenal ulcer is suggested by the observations of Reynolds and McClure,[9] who describe one case in which duodenal ulcer was associated with an hour-glass contraction of the stomach.

In some of the papers referred to here there is a certain amount of confusion as to the site of the ulcers discussed, since the lesion is termed a "peptic" ulcer, and the exact situation is not stated. It is not certain that the conclusions drawn from a study of gastric ulcers can be applied to those of the duodenum, or vice versa.

A careful study of the work of all the authors consulted shows that the views of the majority may be summarized in two hypotheses: namely, that the pain is caused by (*a*) "acid" or (*b*) muscle tension. Some authors have combined these by suggesting that acid causes hypertonus and pylorospasm, and have said that in patients with true achylia pylorospasm never occurs.

In support of the acid hypothesis is the fact that the gastric acidity is high in many patients with duodenal ulcer, and also that relief by the administrations of alkalis is an almost universal experience, at least at some period in each patient's history. The statements of Bonninger, Palmer and others that pain follows the administration of from 100 to 200 cc. of from 0.36 to 0.5 per cent hydrochloric acid on an empty stomach are strongly in its favor. Further, Sippy and Palmer found constant relief by emptying the stomach in such cases, and in these the gastric contents were markedly acid.

Against the acid hypothesis are the few instances on record of patients with duodenal ulcer in whose gastric contents free acid was not found. In the literature there are also reports of many cases of patients with hypochlorhydria. Hurst, Ginsburg and others failed to produce pain by administering from 0.5 to 1 per cent hydrochloric acid, although Ginsburg found that in one patient the administration of 5 per cent hydrochloric acid was followed by intense pain and vomiting. Reynolds and McClure poured 0.36 per cent hydrochloric acid through a tube directly on a duodenal ulcer, producing pylorospasm, cessation

16. Homans, J.: Am. J. M. Sc. **157**:74, 1919.

17. Ortmayer, M.: Gastric Motor Activity in Patients with Peptic Ulcer. Arch. Int. Med. **35**:423 (April) 1925.

of gastric peristalsis, and duodenal antiperistalsis, but no pain. Hardt even found temporary relief from the administration of 0.3 per cent hydrochloric acid. In Palmer's cases, the pain did not appear for several minutes (from six to twenty-eight) after the introduction of the acid.

The first evidence in favor of the muscle tension hypothesis is the tracings of intragastric pressure of Carlson, Ginsburg and Hardt, showing that pain most frequently appears at or just after a contraction of the musculature of the fundus. In the opinion of Rogers and Hardt,[18] such contractions are violent peristaltic waves. Glaessner and Kreuzfuchs and Reynolds and McClure found pylorospasm or certain types of abnormal muscular activity present during pain; the latter showed that these abnormalities were replaced by more nearly normal muscular activities following the administration of alkalis. Poulton passed tubes into the stomach and duodenum of each patient, and ascribed the relief experienced to equalization of the internal pressure. He also introduced air under pressure and increased the pain.

Against the tension hypothesis is Palmer's roentgenographic evidence that peristalsis and pylorospasm appeared and disappeared without relation to pain. Reynolds and McClure observed one patient in whom pain was present with a patent pyloric sphincter, and a moment later pylorospasm set in and the pain vanished. In a patient with chronic duodenal ulcer, Homans found that powerful contraction of the stomach was present without pain and, on the other hand, that the patient experienced pain during a quiescent interval. Ortmayer, using the same technic, was unable to detect any change in the frequency or extent of the contractions of the stomach during the relief of pain by alkalis.

To throw some light on this problem, direct observations were made under the fluorescent screen on the movements of the stomach and duodenum in patients suffering from duodenal ulcer associated with pain at the time of observation. Considerable difficulty was experienced in securing suitable patients for this investigation because many, including, of course, those in the wards of the hospital, had received treatment, such as rest in bed, suitable diet and alkalis, and were now free from pain. By selecting patients attending the outpatient department who had not received treatment, sixteen who were suitable for this investigation were found in a period of two years. Each patient was given a barium meal and was examined fluoroscopically in the standing position as soon as possible after the onset of pain. Immediately after the fluoroscopic examination and while some barium remained in the stomach, a small tube was passed and some of the gastric contents removed and examined chemically.

18. Rogers, F. T., and Hardt, L. L. J.: Am. J. Physiol. **38**:274, 1915.

In all cases the barium had sedimented so that only the shadow of the greater curvature could be made out. An estimate was made of the amount of the meal remaining in the stomach, and it was found that this varied from 5 to 60 per cent. The stomach was now observed for several minutes to see whether peristalsis could be detected in the greater curvature. Ten of the patients were found to exhibit peristaltic waves, which varied considerably in depth and frequency, being classified as slight, good or very good. Barium was not seen to enter the cap in any case.

After the behavior of the stomach was observed for some minutes, pressure was applied on the abdominal wall, and barium was forced through the pyloric canal into the cap. At first considerable difficulty was experienced in filling the cap; later, as the operator became more

Data of Gastric Contents in Sixteen Cases

Case No.	Onset of Pain After Meal (Min.)	Time of Observation After Onset (Min.)	Percentage of Meal in Stomach	Peristalsis	Free Acid	Total Acid	Effect of Forcing Contents into Duodenum
1.....	85	5	20	.....	68	108	Relief
2.....	75	5	5	Slight	42	68	Relief
3.....	105	5	30	None	52	90	Relief
4.....	105	15	30	None	70	94	Relief
5.....	105	30	5	Slight	98	108	Relief
6.....	115	15	40	Very good	68	97	Relief
7.....	40	10	30	Slight	76	90	Relief
8.....	155	10	20	Good	71	82	Relief
9.....	65	30	40	Slight	75	93	Relief
10.....	80	30	40	None	54	79	Relief
11.....	96	10	25	Good	13	40	Relief
12.....	170	15	60	Good	..	..	Relief
13.....	60	105	20	Very good	..	..	Relief
14.....	95	35	15	Good	78	93	No relief
15.....	40	45	60	None	..	..	No relief
16.....	15	15	50	None	..	..	No relief

expert in this manipulation, it was found that the cap could be filled with ease on the first attempt in nearly every instance. Subsequent observations showed that the difficulty encountered in the first attempts was due to spasm of the pylorus induced by massage.

In thirteen of the sixteen cases, it was found that filling the duodenal cap by manual pressure on the abdomen was followed almost immediately by relief from the pain. In three instances the pain vanished completely on the first filling of the cap and did not recur. In five cases the pain vanished completely but recurred in a few seconds. In five cases the acuteness of the pain was lessened, leaving a sense of soreness. In the remaining three cases the pain was not relieved when the gastric contents were forced into the duodenum. These are discussed later in the paper. In several of the cases the patient volunteered the statement that his pain had been relieved; in the others, the question: "How is the pain now?" met with the response: "It is gone," or "It is much better."

The accompanying table shows the time of onset of the pain, the time of observation, the principal fluoroscopic manifestations and the free and total acidity of the gastric contents in these sixteen cases. The last three patients in the list differed from the others, and their protocols and the protocol of an additional patient are given in full.

PROTOCOLS OF LAST THREE CASES IN TABLE

CASE 14.—The patient had had epigastric pain from one-half to two hours after meals at intervals for twelve years.

9:50 a. m. A barium meal was given. The duodenal ulcer close to the pyloric sphincter was confirmed by a series of roentgenograms.

11:55. The patient had had pain for the last thirty minutes with headache. Both the pain and the headache were intermittent.

11:58. Fifteen per cent of the barium meal remained in the stomach. The rate of peristalsis was fairly good, but not nearly as strong as it had been at 9:50 to 10. The pain came and went without any change in peristalsis.

12:02. By means of manual pressure on the abdomen, a little barium was squeezed past the pyloric sphincter. Much pressure was required. The cap could not be filled, but a streak of barium was seen to pass into the second portion of the duodenum. No change in sensation occurred.

12:03 to 12:07. The manipulation was repeated twice. The pain kept coming and going, and was not influenced by pressure or squeezing over except at the last manipulation when, discomfort not being present, squeezing over was followed by pain. Frontal headache also came and went, roughly parallel to the occurrence of epigastric pain.

12:20. A duodenal tube was passed.

12:21 to 12:27. Sixty cubic centimeters of opalescent, white gastric contents containing a little mucus was removed. Free acid was 78 and total acid, 93.

CASE 15.—At 10:10 a. m., a barium meal was given. The presence of a duodenal ulcer was confirmed by a series of roentgenograms.

11:25. Soreness had been noticed in the epigastrium for the last thirty-five minutes while the patient had been lying down.

11:35. Sixty per cent of the meal remained in the stomach. Peristalsis did not occur. Soreness was not present now.

11:38. Still peristalsis and soreness were not present. Barium was pressed into the cap with moderate difficulty. Soreness ensued. The soreness came and went. Sometimes barium could be pressed into the cap and sometimes it could not. (It was concluded at the time that the soreness was not wholly due to spasm.) The obstruction encountered was not proximal to the pyloric sphincter, since the shape of the gastric shadow was normal. When the gastric contents could be pressed into the duodenum during the soreness, this was eased. Vigorous manipulation apparently caused soreness. There was a constant residue in one small spot of the cap (crater?). Only once was a peristaltic wave seen.

11:55. The observation was concluded.

CASE 16.—The patient was 45 years of age.

9:45 a. m. A barium meal was given. The presence of a duodenal ulcer was confirmed by a series of roentgenograms.

10:00. Pain commenced.

10:15. Fifty per cent of the meal remained in the stomach. The stomach was seen to be in the pelvis, the greater curvature being about 4 inches (10 cm.)

below the intercristal line. Peristalsis did not occur. When the stomach was raised by pressure on the abdomen, the pain vanished. When the pressure was released the pain returned. This was repeated twice with similar results.

10:23. The patient put on his abdominal belt, and at once the pain was eased. He stated that he did not feel pain when lying down.

With reference to the observation of Reynolds and McClure [9] that spasm of some part of the stomach may be associated with the pain in some patients with duodenal ulcer, the following is the only instance I have seen which suggests this:

CASE 17.—The patient had had attacks of epigastric pain about two hours after meals for several years. The pain was relieved by food.

9:45 a. m. A barium meal was given. Fluoroscopic examination showed a constantly deformed cap. This was confirmed by a series of roentgenograms.

11:50. Epigastric pain commenced.

12:05. The stomach was empty, as seen under the fluoroscope. The pain came and went.

12:10. The patient was given a barium meal of 8 ounces (227 Gm.).

12:11. Gastric peristalsis did not occur, but a definite midgastric constriction was noticed. Pain was still present.

12:13. The constriction disappeared, as did the pain also. Peristalsis began, and the cap filled.

12:14. The peristaltic movement was strong. The cap was filling.

12:20. Well marked peristalsis was present. The cap filled at the approach of each wave. The patient did not feel any pain.

COMMENT

The important fact which emerged from this investigation was that in patients with duodenal ulcer suffering from pain at the time of observation, filling of the duodenal cap with gastric contents by manual pressure on the abdomen was followed by relief from the pain in thirteen of sixteen cases.

In eleven of these sixteen cases the gastric contents were strongly acid, the free acidity varying from 42 to 98, and the total acidity from 68 to 108. In all but one of the eleven cases just described the introduction of the strongly acid contents of the stomach into the duodenal cap was followed by relief from the pain. There would, therefore, appear to be no direct relationship between the acidity of the gastric contents and the occurrence of pain in patients with duodenal ulcer. However, the almost universal experience of relief from the pain of duodenal ulcer by the administration of alkalis suggests that acid in some manner may be a factor in the production of pain.

The activities of the musculature of the stomach and duodenum in their relationship to pain may be considered from the following standpoints: (1) peristalsis; (2) abnormal local contractions (for example, spasmodic hour-glass); (3) general tonic contractions, such as the gradual contraction of the stomach as the contents pass out; (4) resis-

tance to distention ("hold-on"); (5) relaxation (active or passive). The last three may be regarded as manifestations of "tone" or "postural activity" (Sherrington).

The overaction of peristalsis, local or general contractions, or resistance to distention might produce pain, whereas depression of these activities might relieve pain. Relaxation might abolish pain.

In this investigation, except in case 17, in which localized midgastric contraction was present, there was no relationship between peristalsis, abnormal local contraction, general tonic contraction or resistance to distention and pain in regard to the stomach. The fact that the pain was not in waves but was constant is further proof that peristalsis was not the cause. It is therefore unlikely that the pain in duodenal ulcer is due to overaction of the musculature of the stomach.

In regard to the pyloric sphincter, peristaltic activity can hardly have been the factor causing pain, because the pain was constant and did not occur in waves. Neither spasmodic contraction, tonic contraction, nor resistance to distension can be implicated, because in several of the patients the gastric contents could be moved through the sphincter with ease while pain was being felt. This indicates that the sphincter was relaxed and that in all probability the pain was not due to the overaction of its musculature. Support is lent to this view by the observation in case 14 that the pain was not relieved when the gastric contents passed through the pyloric sphincter but did not distend the caput.

It was found extremely difficult to make observations on peristalsis in the duodenum as in every instance the contents passed through quickly. However, the pain was constant and did not occur in waves, so it is presumed that the pain was not due to duodenal peristalsis.

That abnormal local contraction of the caput is not the sole cause of the pain is evidenced by the constant presence of deformity of the caput in many persons with duodenal ulcer when pain is absent. This deformity is due in part to the contraction of scar tissue, but also in part to muscular contraction. This is obvious from a comparison of the appearance of an ulcerated duodenum in roentgenograms made after a barium meal, with the relaxed condition of the duodenum as seen on the operating table. It is possible that such an abnormal local contraction may by sudden or excessive action give rise to pain, because of the fact that it is involved in a general contraction of the caput.

The evidence in favor of the existence of a general contraction of the caput in these cases is as follows:

The caput was usually empty, and even when it contained barium it was of small caliber, and the barium rushed through in a narrow stream. The relief of pain, following the filling of the caput by manual pressure on the abdomen, suggests that relaxation was the cause of the relief

This is corroborated by the observations in case 14, in which the gastric contents passed through the caput, but did not fill it, and the pain remained.

Therefore, the hypothesis arises that the relief of pain is due to relaxation of the musculature of the caput, and conversely, that the pain is due to overaction of the duodenal caput with or without abnormal local contraction or implication of the pyloric sphincter.

There remains the explanation of the absence of relief in the last three cases in the table. Case 14 is explicable on the ground that the caput was not filled by the manipulation. In cases 15 and 16 the pain was postural, and in all probability was due to traction on inflamed peritoneal attachments.

CONCLUSIONS

1. The presence or absence of gastric peristalsis does not bear any relation to the occurrence of pain in duodenal ulcer.

2. Pain in duodenal ulcer is nearly always relieved by squeezing gastric contents into the duodenal caput.

3. Pain in duodenal ulcer is not directly due to the acidity of the gastric contents.

4. The relief from pain in duodenal ulcer is due to relaxation of the musculature of the duodenal caput. Pain in duodenal ulcer is due to sustained contraction of the duodenal caput.

RENAL FUNCTION TESTS WITH SODIUM THIOSULPHATE AND SODIUM IODIDE

AN EXPERIMENTAL COMPARISON WITH THE PHENOLSULPHONPHTHALEIN TEST *

ADOLPH BOLLIGER, PH.D.
DETROIT

As reported elsewhere,[1] chronic interstitial nephritis is readily produced in dogs by direct roentgen-ray irradiation of the kidneys. The functional aspect of this experimental disease, as far as the usual tests are concerned, has also been recorded,[2] and reference has been made to a combined renal function test consisting of the injection of sodium thiosulphate, sodium iodide and phenolsulphonphthalein. The present investigation deals with the excretion of these three substances throughout a course of experimental disease of the kidneys. Subsequently, this combined test was also applied to a large group of normal animals. Observations on normal animals led to an investigation concerning the behavior of normal pregnant animals toward the combined test. The latter are also reported in this paper.

Nyiri [3] called attention to the usefulness of sodium thiosulphate as an agent for tests of renal function. He also proposed a combination of the sodium thiosulphate tests with the two hour sodium iodide test by injecting the two substances together.[4] In the work reported here, Nyiri's combination, previously used only in clinical diagnosis, was adopted and a third test was added to this combination, the phenolsulphonphthalein test, as described by Rowntree and Geraghty.[5]

METHODS

A solution was made up containing 1 Gm. of sodium iodide, U. S. P., 1 Gm. of sodium thiosulphate, U. S. P., and 6 mg. of phenolsulphonphthalein in 10 cc. of water. The animal was catheterized, and 10 cc.

* From the laboratories of the Henry Ford Hospital.

1. Hartman, F. W.; Bolliger, A., and Doub, H. P.: Experimental Nephritis Produced by Irradiation, Am. J. M. Sc. **172**:487 (Oct.) 1926.

2. Hartman, F. W.; Bolliger, A., and Doub, H. P.: Functional Studies Throughout the Course of Roentgen-Ray Nephritis, J. A. M. A. **88**:139 (Jan. 15) 1927.

3. Nyiri, W.: Die Thiosulfatprobe, Wien. klin. Wchnschr. **35**:682, 1922.

4. Nyiri, W.: Kurzfristige, einzeitige Nierenfunctionspruefung, Wien. Arch. f. inn. Med. **9**:511, 1924.

5. Rowntree, E. G., and Geraghty, J. T.: The Functional Activity of the Kidney, J. Pharm. & Exper. Therap. **50**:580, 1910.

of the solution was injected intravenously. Two hours after injection the animal was catheterized again, and the bladder was irrigated in order to obtain the complete output. The two hour sample of urine, including the wash water, was then made up to a known volume and examined for its sodium thiosulphate content, its iodine content and its phenolsulphonphthalein content.

Nyiri [3] described a technic for the determination of sodium thiosulphate and sodium iodide. His technic was modified in these experiments somewhat in order to shorten his rather lengthy procedure for the determination of the iodine output and in order to improve the determination of sodium thiosulphate. To remove iodine absorbing substances, Nyiri purified the urine with pure charcoal for from two to three minutes. Unfortunately, charcoal rapidly absorbs sodium thiosulphate. To remove this source of error, Lloyd's reagent was substituted. This does not absorb any appreciable amount of sodium thiosulphate even if it is left for many hours. Sodium thiosulphate was then determined by titration with hundredth-normal iodine solution.

The same urine fraction which has been purified with Lloyd's reagent can also be used for the determination of iodine. This saves the removal of iodine absorbing substances with 2 per cent ferricchloride as proposed by Singer [6] and adopted by Nyiri, and iodine is determined directly, according to the method of Singer, by liberation with nitrous acid and extraction of carbon bisulphide. In the work reported here, for convenience, carbon bisulphide was replaced by carbon tetrachloride and the iodine output determined colorimetrically with a set of standards in a comparator. A titration method that consumed considerable time was proposed by Nyiri for determining the liberated iodine in carbon bisulphide.

The tests were carried out in the following manner:

Two hours after the initial injection into a dog, 80 cc. of urine, for example, was obtained by catheterization. The bladder was irrigated, the wash water was included and the entire volume was made up to 200 cc. The specimen was at the same time acidified with dilute sulphuric acid. The phenolsulphonphthalein serves as an indicator for the requisite acidity, turning yellow as soon as the specimen is acid. Twenty cubic centimeters (one tenth) of the entire volume of urine was made up to 100 cc., and alkalinized, and the phenolsulphonphthalein was read against a set of standards. The remainder of the urine was shaken with about 5 Gm. of Lloyd's reagent and filtered. Twenty cubic centimeters of the filtrate was used for determination of the sodium thiosulphate output. This fraction was titrated with hundredth-normal iodine solution, starch being used as an indicator. The end-point is sharply indicated by a changing of the yellow solution to a bluish green, which has to remain thus for at least two seconds. The other 20 cc. of the filtrate was used for the determination of the iodine. This fraction is trans-

6. Singer, H.: Methodisches zur quantitativen Bestimmung des Jodkali, Ztschr. f. klin. Med. **48**:157, 1903.

ferred to an extraction funnel. About 7 cc. of carbon tetrachloride was added with a few drops of a solution of sodium nitrite in concentrated sulphuric acid. The liberated iodine was extracted with the carbon tetrachloride, care being taken not to shake too hard in order to avoid emulsion. The urine was again extracted with a smaller portion of carbon tetrachloride until iodine was no longer demonstrable. The lavender colored carbon tetrachloride solution was made up to a known amount and compared with standards made up by dissolving known amounts of iodine with carbon tetrachloride.

It is well known that hundredth-normal iodine solution is not stable over a long period. This solution may be standardized quickly against the thiosulphate-iodide-phenolsulphonphthalein solution used for this functional test. The number of cubic centimeters of hundredth-normal iodine solution required by 20 cc. of 0.5 per cent solution of the original combined substances (10 cc. test solution diluted to 200 cc.) will give that figure to be used in calculating the percentage of thiosulphate present in 20 cc. of urine, the volume of which has previously been made up to 200 cc.

As has been pointed out previously, Lloyd's reagent does not absorb any sodium iodide or sodium thiosulphate. Further, this reagent does not absorb any of the phenolsulphonphthalein dye. The phenolsulphonphthalein content could also be determined to advantage on a urinary filtrate treated previously with Lloyd's reagent, because Lloyd's reagent removes to a large extent other coloring matters and colloidal suspensions which do interfere with the estimation of the phenolsulphonphthalein output.

The combined injection of sodium thiosulphate, sodium iodide and phenolsulphonphthalein will be spoken of as the combined test in the following experiments. It was applied to (*A*) normal dogs and dogs with extrarenal lesions; (*B*) normal dogs during gestation, and (*C*) dogs with experimental nephritis produced by deep roentgen rays.

EXPERIMENTS

A. Normal Dogs and Dogs with Extrarenal Lesions.—Table 1 includes a series of fifteen normal female animals to which the combined test has been applied. The thiosulphate output in two hours varies from 50 to 66 per cent after the injection of 1 Gm. of sodium thiosulphate, U. S. P. I consider this as the normal range of thiosulphate output for dogs. This table further includes a depancreatized dog, a dog with distemper and a morphinized animal. The thiosulphate output of the animals with extrarenal lesions lies also between the normal range, i. e., from 50 to 66 per cent. The iodine output after the administration of 1 Gm. of sodium iodide varies from 0 to 95 mg. in two hours. The majority of the observations showed an output of between 40 and 80 mg. in two hours.

Table 2 represents a dog which had, during the period of observation, extensive roentgen-ray treatment over the chest. The animal developed a lesion of the heart as proved by electrocardiograms and at autopsy. The electrocardiograms showed tachycardia and auricular flutter, and at autopsy hemorrhages and hyaline degeneration were found throughout the right auricle. Before and during the experiment, several combined tests were performed over a period of three months. The phenolsul-

TABLE 1.—*Results of Tests in Normal Dogs and Dogs with Extrarenal Lesions*

No.	Phenolsul-phonphthalein (Per Cent)	Iodine Excretion (Mg.)	Sodium Thiosulphate (Per Cent)	Urea	
1	70	40	56.4	15.4	
1	78	203	55.6	11.4	Two days after irradiation over left kidney
2	65	45	53.5	....	
2	70	78.7	51.0	....	
3	60	50	58.5	....	Depancreatized; blood sugar, 430 Gm.
4	70	70	64	....	
4	70	50	63.0	....	
5	70	50	58	....	
6	70	45	59.5	....	
7	65	56	61.7	....	
8	65	0	62	....	
8	65	80	50	....	Distemper; died three days later
9	65	61	47.3	....	
10	70	61	63.4	....	
10	70	95	65.9	....	After morphine, 1 grain (0.065 Gm.)
11	70	0	53.5	....	
12	70	5	55.3	....	
13	60	45	51.2	....	
14	70	55	55	....	
15	65	60	56	....	
16	75	25	54	....	
17	70	80	62	....	

TABLE 2.—*Results of Tests in Dog with Cardiac Lesion*

Date	Phenolsul-phonphthalein (Per Cent)	Sodium Thiosulphate (Per Cent)	Iodine Excretion (Mg.)	Urea
5/20/26	70	63	61	15.4
5/27	70	66	95	....
7/7	70	71	28	14.5
7/13	70	67	600	18.2
8/24	65	72	544	14.1

phonphthalein output did not change. The sodium thiosulphate output became increased in the last month of the experiment. The excretion of iodine was found to be as high as 600 mg. during the period when the animal showed marked tachycardia.

Table 3 represents an animal with a persistent albuminuria which was followed over a period of three months. The animal appeared to be healthy in every respect, and an explanation for the albuminuria could not be found. The phenolsulphonphthalein output remained between normal limits throughout the whole experiment. The sodium thiosul-

phate output did not reveal any functional disturbances, and the iodine excretion varied from 11 to 230 mg. in two hours.

B. Normal Dogs During Gestation.—The following observations were made on three animals which were pregnant when obtained for the laboratory: They were under observation for a number of months and bore an apparently full term litter. Two of the animals were considered entirely normal, but the third animal had had one kidney removed before observations were started.

Chart 1 illustrates a large normal dog which showed, fifty-one days before delivery, a phenolsulphonphthalein output of 70 per cent, a thiosulphate excretion of 60 per cent and an iodine excretion of 57 mg. Up to delivery six more combined tests were done at varying intervals. The phenolsulphonphthalein test did not show any consistent fluctuations but remained within normal limits throughout the experiment. Forty-three days before delivery the sodium thiosulphate output was markedly

TABLE 3.—*Results of Test in Dog with Persistent Albuminuria*

Date	Phenolsulphonphthalein (Per Cent)	Sodium Thiosulphate (Per Cent)	Iodine Excretion (Mg.)	Urea
3/22/26	65	52	90	15.4
3/27	70	55	55	12.1
3/31	70	57	109	....
5/5	70	52	128	12.0
5/7	70	50	11	12.1
5/10	70	56	36	11.0
5/22	75	60	90	17.7
6/8	72	63	44	....
6/18	70	52	230	17.9
6/30	65	60	27	12.6

diminished, i. e., 46 per cent, and the iodine output was somewhat diminished also. Thirty-five days before delivery the sodium thiosulphate output was only 40 per cent, and there was no iodine output during the two hours of the test. Twenty-one days before delivery the sodium thiosulphate output was at its lowest level, i. e., 33 per cent, and the iodine output was still 0. Eight days before delivery the thiosulphate output started to increase again (37 per cent). The test for iodine became positive, i. e., 28 mg. was present. Eighteen hours before delivery the thiosulphate output was nearly normal, i. e., 47 per cent, and the iodine excretion was 156 mg. The animal was delivered of nine living pups and had a normal postpartum course. One month after delivery, the sodium thiosulphate output was found within normal range and the iodine output was 92 mg. Two weeks later, the output of thiosulphate and of phenolsulphonphthalein was still found to be within normal range.

Chart 2 represents a similar animal. About one month before delivery, a marked depression in the sodium thiosulphate output was found, with a recovery to normal after delivery. The iodine output was some-

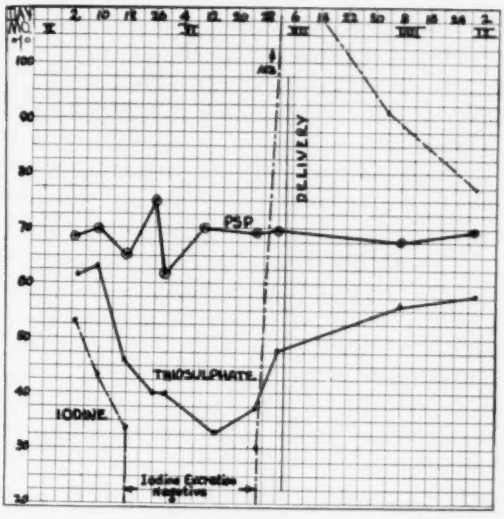

Chart 1.—Results of test in a large normal pregnant dog. In this chart and in charts 2, 3 and 4, *PSP* indicates phenolsulphonpthalein.

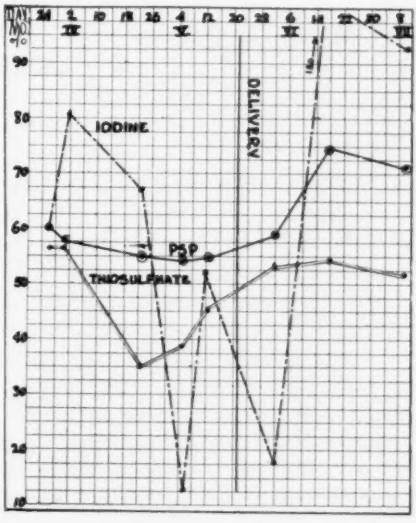

Chart 2.—Results of test in an animal similar to the one shown in chart 1.

what irregular, reaching the low level of 12 mg. about two weeks before delivery; about one week before delivery, the iodine output was 54 mg., and dropped to 20 mg. about twelve days after delivery. In this case, also, a slight depression in the phenolsulphonphthalein output could be made out (53 per cent at its lowest point), coincident with depression in the thiosulphate output.

Chart 3 represents the dog in which the left kidney was removed a short time before impregnation. The thiosulphate output was found to be depressed when the observations were started, about one and one-half months after operation and forty-six days before delivery. Thirty-three days before delivery the sodium thiosulphate output was only 30 per cent, and this dropped down to 23 per cent in the next few days. A week later, there was a slow, steady improvement in the puerperium, and the output of thiosulphate had increased to 48 per cent nineteen days after delivery. A depression in the iodine output was found about five weeks before delivery. The phenolsulphonphthalein output was also somewhat depressed, as in the previous experiment.

C. Dogs with Experimental Nephritis Produced by Deep Roentgen Ray.—The pathologic changes in nephritis as produced by deep roentgen rays have already been described. The condition has been subdivided, for the purpose of study, into the acute, subacute and chronic stage. The combined test was applied to all these stages, as can be seen in chart 4. This chart demonstrates a moderately rapid progressive nephritis which was produced by irradiation of both kidneys through the abdominal wall. The course of the disease is well depicted by the phenolsulphonphthalein output. Nearly one month after irradiation the phenolsulphonphthtalein output remained within normal levels, and from previous experience this might be considered the acute and the subacute stages of the disease. During the next fourteen days a marked depression of the phenolsulphonphthalein output was noticed, reaching 35 per cent about one and one-half months after irradiation. For the next two months the fluctuations were moderate, and this might be considered as the chronic stage. During the last month of the animal's life, a further marked depression was noticed, which could be considered as the late chronic stage. The thiosulphate output was practically parallel with the output of phenolsulphonphthalein throughout the disease. A subnormal thiosulphate output was found in the subacute stage, while the phenolsulphonphthalein output was still normal. The parallelism between the thiosulphate output and the phenolsulphonphthalein output was found throughout until the late chronic stage, when the phenolsulphonphthalein output became more depressed than the thiosulphate output. The iodine output showed large fluctuations and there was an agreement only between the phenolsulphonphthalein and the iodine

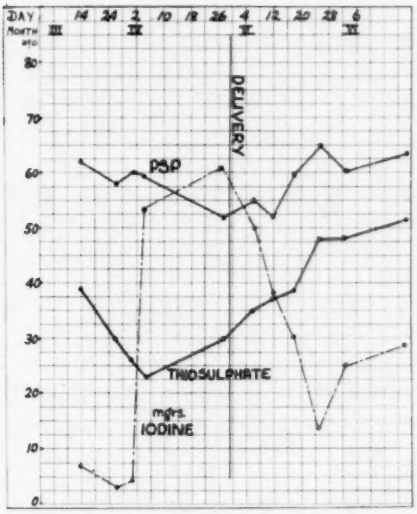

Chart 3.—Results of test in a dog in which the left kidney was removed a short time before impregnation.

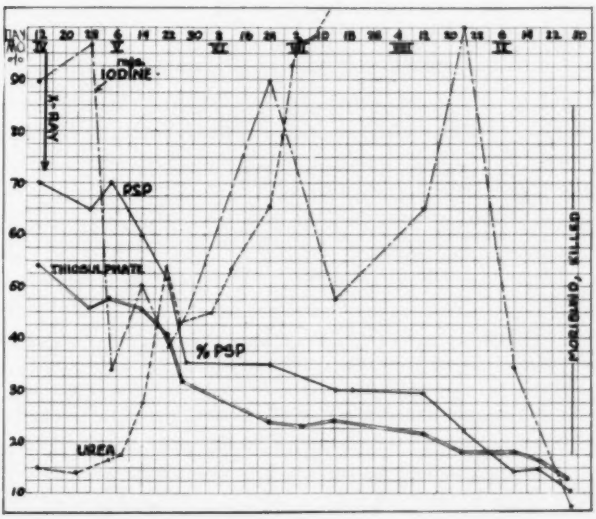

Chart 4.—Results of combined test as applied in acute, subacute and chronic stage.

output in the terminal stage, both being low. The iodine excretion was found to be high soon after irradiation.

Chart 5 represents an animal with a rapidly progressing nephritis terminating in uremia. The left kidney was irradiated directly through a surgical incision. A month later the right kidney was removed and a

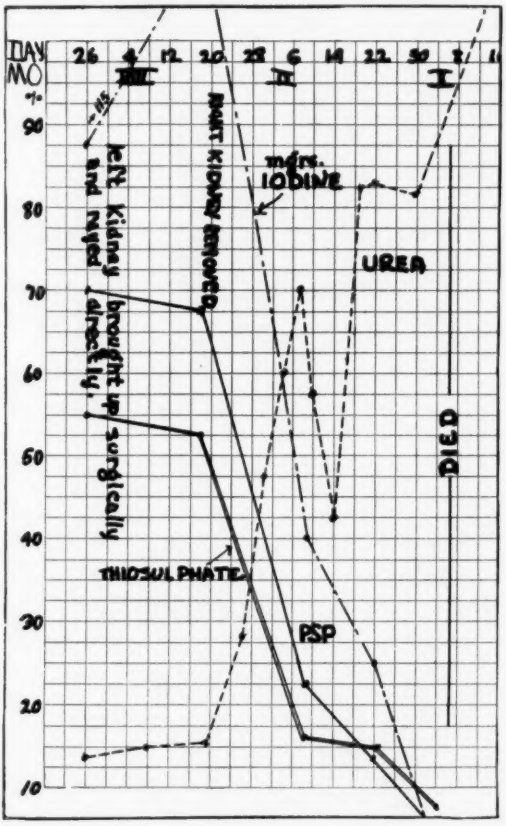

Chart 5.—Results of test in an animal with a rapidly progressing nephritis terminating in uremia.

sudden fall in the phenolsulphonphthalein and thiosulphate outputs was noticed together with a rapid increase in the urea nitrogen content of the blood. As confirmed in a number of similar experiments, the directly irradiated kidney becomes fibrosed rapidly, and a lethal insufficiency is produced as soon as the nonirradiated kidney is removed. In spite of the short irradiation, this animal died a month after removal of the non-

irradiated kidney. The same parallelism between thiosulphate and phenolsulphonphthalein excretion was found in rapidly progressing nephritis. In the late stage, ten days before death, the thiosulphate output became more depressed than the phenolsulphonphthalein output. Two days before death, the phenolsulphonphthalein output was 2 per cent and the thiosulphate output was 6 per cent. In this type of experiment, the iodine output also is roughly parallel with the phenolsulphonphthalein and thiosulphate outputs. The iodine output increased after irradiation and after removal of the nonirradiated kidney. The iodine output dropped to 40 mg. twenty-four days before death and to 25 mg. ten days before death and only a trace was present two days before death.

TABLE 4.—*Results of Test in Dog with Slowly Progressing Interstitial Nephritis*

Date	Phenolsulphonphthalein (Per Cent)	Sodium Thiosulphate (Per Cent)	Iodine Excretion (Mg.)	Urea	
1/29/26	65	..	..	14	
1/29	Irradiation over both kidneys				
3/23	45	39	12	13.5	Distemper and mangy
3/27	50	39	10	....	
3/31	45	38	24	12.6	
4/3	55	40	24	18.7	
4/28	50	43	43	....	
5/5	50	40	5	14	
5/13	52	43	20	..	
5/21	70	43	28	19.6	
6/2	50	36	70	28.5	
6/7	45	26	33	31.8	
6/24	45	25	80	35	Carbon dioxide — 53
7/14	55	34	64	35	
8/9	55	34	30	42	
8/22	40	28	..	41	
9/30	55	34	..	45	Carbon dioxide — 51

Table 4 represents a dog with a slowly progressing interstitial nephritis. Roentgen-ray irradiation was given once over both kidneys through the abdominal wall. About two months after irradiation the experimental disease became complicated by distemper and mange, but the animal recovered from these complicating factors, and the disease took the slow path of chronic interstitial nephritis as frequently seen in human beings.

The phenolsulphonphthalein output was found to be depressed as soon as observations were started, about a month after irradiation. With a few exceptions, the output of dye averaged about 50 per cent during the next six months of observation. The sodium thiosulphate output was markedly depressed during the period of distemper but increased somewhat and averaged about 30 per cent in the last three months of the experiment. The excretion of iodine was inconsistent as was seen in other experiments of this type, but the amounts of urea nitrogen began to increase slowly during the last four months of observation.

COMMENT

Nyiri described the two hour sodium iodide test as a simple, practical test of renal function. This statement is based on fifty-four observations of normal patients without renal disease and on twenty-six patients with renal insufficiency. The observations on dogs in these experiments do not substantiate those of Nyiri. Animals without renal involvement showed great variations in the iodine output, and animals with proved disease of the kidneys frequently did not show any relation between the state of the disease and the quantitative iodine output two hours after intravenous administration. There was an agreement only between the iodine excretion and an existing renal insufficiency in the late stages, but it was found that the test did not have any diagnostic value in experimental chronic nephritis of dogs.

The hypothesis of Nyiri and earlier workers that the kidneys are the main factor in the urinary excretion of sodium iodide was shown to be correct only in the late stages. The excretion of iodides was frequently not taken up for two or more hours after the intravenous administration in apparently normal animals. After the excretion had started, whether it was delayed or occurred immediately after administration, frequently a relation between the rate of excretion and the concentration of sodium iodide in the blood and tissues could not be demonstrated. Finally, the entire time required to eliminate completely the injected sodium iodide did not give any information regarding activities of the kidney. Some other activities of the body, as shown, for example, in pregnancy, seem to have a far greater influence on the excretion of sodium iodide during the first two hours and also in later periods after the injection of sodium iodide. It is thought that this simple and accurate procedure may find its application in another field.

Like sodium iodide, sodium thiosulphate is found in the normal animal in small amounts; however, it does not follow the excretory properties of sodium iodide but shows a striking similarity in its excretion curve to phenolsulphonphthalein in all experiments with experimental chronic nephritis. Whether the depression of sodium thiosulphate as seen during pregnancy is also accompanied by a similar depression of the phenolsulphonphthalein output is not clear from these experiments, but this discrepancy may be explained by the fact that small functional changes in the kidneys are usually more accurately registered by the thiosulphate test than by the phenolsulphonphthalein test. This is mainly due to the following two facts: first, the thiosulphate output is determined by a more accurate procedure than the phenolsulphonphthalein output, i.e., titration of standardized iodine solution; second, thiosulphate injected intravenously in unchanged form is practically completely excreted in two hours by the normal kidney and by the kidney in which

excretion is insufficient. Thiosulphate that is injected but not excreted is oxidized to sulphate and is excreted as such.

Of course, it may just as well be assumed that the depression of the thiosulphate excretion during pregnancy, as described in three animals and as observed in the meantime on two other dogs, is not at all or only partly connected with the activity of the kidney. The depressed excretion may be considered as the expression of the altered metabolism of pregnancy and may have a useful application in the diagnosis of pregnancy.

On the other hand, it should also be pointed out that the sodium thiosulphate furnishes results averaging from 2 to 3 per cent above the theoretical value. This is due to the fact that the iodine combining substances of the urine are not entirely removed either by treatment with Lloyd's reagent or charcoal. There is a variation in the remaining amount of iodine combining substances in the different urines, in general, following the specific gravity of the urine. At attempt was made to overcome this difficulty by diluting all urines up to a standard amount and titrating at about the same p_H. The small possibility of error seems to be well corrected by these procedures, as can be seen by the consistency of results in the protocols. On the other hand, the fact that the results obtained are somewhat too high may explain the higher output of sodium thiosulphate as compared to phenolsulphonphthalein in renal insufficiency that has progressed far. A thiosulphate output of 0 is rarely encountered.

Nyiri proposed a correction for this inaccuracy by determining the iodine combining power of urine (treated accordingly) previous to the experiment. I consider this correction only a complication of an experimental procedure, since the urine obtained after administration of thiosulphate and water (diuresis) will have other properties than urine obtained previous to the test.

Only about two thirds of the dosage as originally proposed by Nyiri was injected. He used 1 Gm. of anhydrous sodium thiosulphate, and I injected 1 Gm. of sodium thiosulphate U. S. P. containing 6 molecules of water of crystallization or only 0.68 Gm. of anhydrous sodium thiosulphate. This dosage could be reduced further without impairing the accuracy of the results, but it might be pointed out that in these experiments harmful effects, even in animals in which the renal insufficiency had progressed far, were never observed. The diuresis produced immediately after the administration of sodium thiosulphate is of decided value in experimental work, since water does not have to be administered by stomach tube in order that a sufficiently large quantity of urine may be obtained. Diuresis itself does not vitiate the results of the test, since the observations in animals with spontaneous diuresis in the earlier stages of chronic interstitial nephritis show consistent results.

After the phenolsulphonphthalein test was added to the combined renal function test of sodium iodide and sodium thiosulphate, the sodium iodide test was found to be of minor value in tests of renal function. Now, I am using a combination of the sodium thiosulphate test and the phenolsulphonphthalein test. This combination was found satisfactory in experimental work on animals.

I think that this combination will also be of help in clinical work in spite of the fact that the two hour sodium thiosulphate excretion is remarkably smaller in normal human beings than in normal dogs (from 30 to 40 per cent). Nyiri and Eskelund reported gratifying results in clinical cases.[7]

SUMMARY

1. A combination of three renal function tests, consisting of the sodium thiosulphate test, the sodium iodide test and the phenolsulphonphthalein test, was studied experimentally. It was applied to normal, pregnant and nephritic dogs and to dogs with extrarenal lesions.

2. The sodium thiosulphate test is found to be a specific quantitative test for experimental renal insufficiency; it gives essentially the same information as the phenolsulphonphthalein test. It is also somewhat more accurate and may better detect slight lesions in the kidneys.

3. Pregnant dogs show a depression in sodium thiosulphate output.

4. The two hour sodium iodide test is of little value in tests of renal function.

---

7. Eskelund, V.: Kidney Function Test with Sodiumthiosulphate, Hospitalstid. **68**:217, 1925.

EFFECT ON BASAL METABOLISM OF LIGATING LOWER EXTREMITIES *

ANNE TOPPER, M.D.
AND
HANNAH MULIER, M.D.
NEW YORK

There is a law of surface energy which says that the production of heat in different animals is essentially constant per unit of body surface. The idea that there is an intimate relationship between body surface and production of heat was first observed by French writers [1] as early as 1839. The body surface law was definitely formulated in 1847 by Bergmann.[2] In 1883, Rubner [3] and Richet [4] published almost simultaneously the first modern experimental data on the subject, and, because Rubner's work was considered the more important, the body surface law has since been known as Rubner's law.

In the beginning, most physiologists held the conception of a causal relationship between heat production and body surface. From time to time, however, even the most ardent advocates of the body surface law have admitted discrepancies, and its universal applicability has been challenged. Factors such as age, prematurity, prepubescence, sex, athletic training, level of nutrition and pathologic states cause differences in production of heat which cannot be explained on the basis of differences in body surface. The conception, therefore, of a causal relationship between basal metabolism and body surface has come to be abandoned by most physiologists, and instead, the surface area has come to be considered merely the most exact available biometric measurement of basal metabolism.

Researches point to a simple mathematical relationship between production of heat and many bodily functions, a relationship which may be expressed by the simple formula $P^{2/3}$, or the square of the cube root of the body weight, which formula seems to represent a definite general morphologic law of growth. In 1888, von Hoesslin [5] recognized that the

---

* From the Pediatric Service of Mount Sinai Hospital; chief of staff, Dr. Bela Schick.

1. Sarrus and Rameaux: Bull. Acad. roy. de méd. Paris **3**:1094, 1839. Regnault and Reiset: Ann. de chemie et de physique, ser. 3, **26**:299, 1849.

2. Bergmann, Carl: Ueber die Verhältnisse der Wärmeökonomie der Thiere zu ihrer Grösse, Göttingen, Vendenhoeck und Ruprecht, 1848.

3. Rubner: Ueber den Einfluss der Körpergrösse auf Stoff und Kraftwechsel, Ztschr. f. Biol. **19**:545, 1883.

4. Richet: Recherches de calorimétrie, Arch. de Physiol., ser. 3, **15**:237, 1885.

5. Von Hoesslin: Ueber die Ursache der scheinbaren Abhängigkeit des Umsatzes von der Grösse der Körperoberfläche, Arch. f. Anat. u. Physiol., Physiol. Abteil., 1888.

body surface law was but a single application of this general law of growth. Other workers soon questioned the Rubner law. Voit [6] believed that the production of heat is proportional to the mass of living cells and their power to decompose materials, and should not be identified with body surface. Dreyer [7] called attention to the correlation between the cross-section of the trachea and the aorta and the surface area of the body. Moulton [8] observed that the surface area in cattle is proportional to the total body nitrogen, and therefore to the protoplasmic mass. Peabody and Wentworth [9] found a close agreement between surface area and vital capacity. Pfaundler [10] noted that the Rubner law failed to apply to atrophic individuals whose skin hung in folds. Pirquet [11] looked for a surface other than the outer surface of the body mentioned by Rubner in order to find a simpler measure of the nutritional needs of the body.

Thus it is seen that there are many components of the body nearly proportional to the surface area. It is possible that all body cells show this similar proportionality because they are similarly affected by the metabolism and need of the body for oxygen.

Benedict,[12] who is probably the strongest opponent of the Rubner law, says that basal metabolism is a function of the total mass of active protoplasmic tissue. He believes that "if heat production is proportional to the square of the cube root of the body weight, it is not due to the fact that the surface area determines thermolysis, but that the mass of active protoplasmic tissue with probably the same mathematical relationship to the body weight determines thermogenesis."

Helmreich [13] is in accord with Carl Voit and Benedict in believing that metabolism is determined, not by body surface, but by the active protoplasmic mass. In order to prove this theory, he believes cases

6. Voit, Carl: München. med. Wchnschr. **49**:233, 1902.

7. Dreyer, Ray; and Walker: Proc. Roy. Soc. Med. **86**:39, 1912-1913.

8. Moulton: J. Biol. Chem. **24**:299, 1916.

9. Peabody, Francis; and Wentworth, John A.: Clinical Studies of the Respiration, Arch. Int. Med. **20**:443 (Sept.) 1917.

10. Pfaundler: Körpermasstudien: V. Ztschr. f. Kinderh. **14**, 1916.

11. Pirquet: Sitzhöhe und Körpergewicht, Ztschr. f. Kinderh. **14**:211, 1916; System der Ernährung, Berlin, 1917. Schick, B.: Das Pirquetsche System der Ernährung und seine Gegner, Ztschr. f. Kinderh. **28**:62, 1921.

12. Harris, J. A., and Benedict, F. G.: Biometric Study of Basal Metabolism in Man, publ. 279, Carnegie Inst., Washington, 1919. Benedict, F. G.: J. Biol. Chem. **20**:263, 1915. Benedict and Talbot: Metabolism and Growth from Birth to Puberty, publ. 302, Carnegie Inst., Washington, 1921; publ. 201, 1914; publ. 233, 1915.

13. Helmreich, E.: Die Unabhängigkeit des basalen Kraftwechsels von der Körperoberfläche, Ztschr. f. d. Ges. exper. Med. **53**:578, 1926; Der Kraftwechsel des Kindes, Vienna, Julius Springer, 1927.

should be studied in which a disunion between mass and surface has been affected. In 1916, Pfaundler [10] first suggested the possibility of effecting such a disjunction, but his work involved operative procedure on small animals with long ears and long tails. In 1917, Aub and DuBois [14] studied the metabolism of two legless men to determine whether the Rubner law applied. But they did not have figures before amputation for comparison with those obtained after amputation. Furthermore, amputation creates a pathologic condition.

Helmreich conceived a method of excluding large parts of the body mass from the general circulation without producing a pathologic state, which would at the same time allow a comparison of metabolism before and after such exclusion. His method was as follows:

He ligated an extremity so tightly as to occlude the venous and arterial circulation. In this way, the extremity was withdrawn for the time as an active protoplasmic mass, just as though it had been amputated. The outer surface, however, was not affected, and the nerve connection between the ligated area and the rest of the surface remained unbroken, as was demonstrated in the experiment. If metabolism bears a causal relationship to body surface, it must remain unchanged during the ligation period. If metabolism is a function of active protoplasmic tissue, it must decrease when part of the protoplasmic mass is inactivated through ligation. Helmreich found in all cases a decrease in metabolism which was roughly proportional to the weight of the part ligated, as measured by its volume of water displacement, and not proportional to the surface.

In order to prove that the surface remained intact, Helmreich applied thermal stimuli in the form of ice or ice water to the ligated extremity as well as to the extremity without ligation, and found an increase in metabolism in both cases in response to the external cold.

Helmreich concluded that basal metabolism is a function of the active protoplasmic mass, and not of the body surface. The surface, in its capacity of receptor organ for tactile, pain and thermal stimuli, influences the height of metabolism, but should not be identified with metabolism.

We duplicated Helmreich's experiments. One of us (A. T.) attempted the work with several children, but found that the pain and excitement caused by ligation proved so disturbing emotionally that the children could not remain quiet, and therefore the figures obtained were not truly basal. We then decided to try the experiment on each other.

METHOD

We followed Helmreich's method closely, except that whereas he took two minute readings, we took four or five minute readings. The Krogh calorimeter was used. After a fourteen hour fast, and under the usual resting conditions, a

14. Aub, J. C., and DuBois, E. F.: Basal Metabolism of Dwarfs and Legless Men, Arch. Int. Med. **21**:840 (May) 1917. DuBois, E. F.: Basal Metabolism in Health and Disease, ed. 2, Philadelphia, 1927, P. 119. DuBois, D., and E. F.: A Formula to Estimate the Approximate Surface Area, Clinical Calorimetry, Arch. Int. Med. **17**:863 (June) 1916.

determination of the basal metabolism was made. A half inch rubber ligature was then applied to one or both extremities, high up under the symphysis, so tightly as to occlude the dorsalis pedis artery. The ligature was left on for five minutes, and with the ligature still on, another metabolism test was made. The ligature was then withdrawn, and metabolism tests were made at short intervals until the normal basal metabolism was again reached. This procedure was repeated on each of us on six different days. The right extremity was ligated three times, the left one twice, and both extremities once.

On another occasion, with the ligature applied, the extremity was packed in ice from toes to hip, and determinations of metabolism were made as before. This procedure was followed without ligation another day.

Table 1 shows the effect of ligation on our basal metabolism. Table 2 shows Helmreich's results.

TABLE 1.—*Effect on Basal Metabolism of Ligating the Lower Extremities (Topper and Mulier)*

Date	Part Ligated	Kilograms of Body Weight	Weight of Leg in Kg.*	Proportion of Body Weight	Body Surface, Sq.M.†	Surface of Ligated Part in Sq.Cm.‡	Proportion of Body Surface	Basal Metabolism, Total Calories for 24 Hour Period	Decrease During Ligation	Percentage Decrease
A. T.										
May 26	Right leg	56.8	7.25	12.7%	1.58	2,875	18.2%	1,298	154	11.9
June 6	Right leg	....	....	....	....	.....	....	1,300	150	11.6
9	Right leg	....	....	....	....	.....	....	1,246	135	10.8
14	Left leg	....	....	....	....	.....	....	1,262	158	12.5
28	Left leg	....	....	....	....	.....	....	1,186	150	12.6
Oct. 26	Both legs	....	14.5	25.4	....	5,749	36.4	1,455	435	27.8
H. M.										
April 14	Right leg	72.7	8	11	1.75	3,037	17.4	1,400	148	10.5
21	Right leg	....	....	....	....	.....	....	1,380	160	11.6
May 21	Right leg	....	....	....	....	.....	....	1,390	153	11
June 13	Left leg	....	....	....	....	.....	....	1,344	140	10.4
24	Left leg	....	....	....	....	.....	....	1,388	138	10
27	Both legs	....	16	22	....	6,074	34.8	1,464	294	20

* Measured by volume of water displaced.

† DuBois height-weight formula (DuBois, D. and DuBois, E. F.: A Formula to Estimate the Approximate Surface Area if Height and Weight be Known, Arch. Int. Med. **17**: 863 [June] 1916).

‡ DuBois linear formula (DuBois, E. F.: Metabolism in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1927).

RESULTS WITH COMMENTS

Table 1 shows a decrease in basal metabolism of from 10 to 12 per cent when one extremity was ligated and a decrease of from 20 and 28 per cent when both lower extremities were ligated. This decrease in basal metabolism was roughly proportional to the mass ligated and not to the surface.

The decrease in metabolism lasted only as long as the mass remained ligated. As soon as the ligature was removed, there was an increase in basal metabolism above the normal level, and only after ten minutes did the metabolism return to normal. Helmreich explains this increase above normal by the oxidation of a mass of blood and lactic acid withheld during ligation. The lactic acid had been formed in the muscles of the ligated extremity as a result of local anemia.

Charts 2 and 3 show how the body surface, in its function as a receptor organ for thermal stimuli, can influence the height of metabolism. Cold applied to the surface causes an increased production of heat in the body. When the external cold is removed, the basal metabolism returns to the normal level.

When cold was applied to the ligated extremity (chart 3), there was an increase in metabolism, but as soon as the ligature was removed, instead of a return to normal, the metabolic rate sank below the normal and did not return to the normal level until later. Helmreich explains this drop below the normal level by the theory that a mass of cold blood, withheld during ligation, rushes into the general circulation, depresses the temperature of the blood and thus causes a lowering of metabolism.

TABLE 2.—*Effect on Basal Metabolism of Ligating the Lower Extremities (Helmreich)*

Subject	Date	Part Ligated	Body Weight, Kg.	Leg Weight, Kg.*	Proportion of Body Weight, per Cent	Basal Metabolism, Cc. Oxygen	Decrease During Ligation	Percentage Decrease
A. S.	Feb. 27	Right leg	74.3	10	13.5	342	30	8.7
K. G.	Mar. 1	Left leg	42	5.8	13.7	256	28	11.1
	4	Right leg	....	5.73	13.5	260	33	12.6
	13	Left leg	....	....	....	259	29	11.1
	May 9	Left leg	45.3	....	....	305	38	12.5
	9	Left leg	....	....	....	305	43	14
	19	Both legs	45.8	11.52	25.1	305	60	19.6
R. L.	Mar. 15	Left leg	33.6	4.35	12.8	221	30	13.5
E. S.	Mar. 17	Right leg	27.3	3.07	11.1	185	19	10.7
H. F.	May 22	Left leg	39.9	....	....	238	26	10.8†
H. W.	May 17	Left leg	33.8	....	....	253	23	9

* Measured by volume of water displaced.
† Herter's infantalism with large abdomen and thin legs.

From our experience, we cannot recommend that this experiment be used with children as subjects. Ligating both extremities to the point of occlusion of the artery, and packing an extremity in ice is an unpleasant and even painful experience, and we needed to exercise self-control in order to lie quietly during the experimentation period.

The experiment does, however, furnish a way of bringing about an exclusion of blood from large parts of the body without creating, apparently, a pathologic state, and allows of comparison of metabolism before, during and after such exclusion.

Our results are in accord with those of Helmreich. This experiment was performed independently and in several ways more accurately than Helmreich's experiments. The periods of observation were longer, the subjects being adults instead of children; and the experiment was repeated frequently on the same person. The observations in themselves would seem to support the view taken by Helmreich that basal metabolism is independent of body surface, but is rather dependent on active

protoplasmic mass. The concordance with Helmreich's results might be construed to give further support to this idea.

Claim to originality is not made in the observations recorded. They are not submitted as conclusive. As far as they go, they seem to imply that basal metabolism does not have any causal relationship with body surface (Rubner), but rather depends on the amount of active protoplasmic tissue, varying with the mass of active cells, and the nervous stimulus to cellular activity existing at the time the test is made (Benedict).

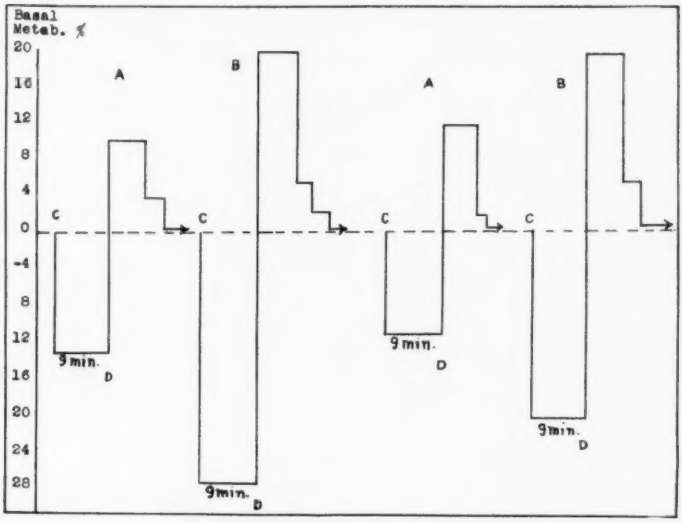

Chart 1.—Effects of basal metabolism. The first two curves represent the experiments of Topper, and the second two represent those of Mulier. *A* indicates that one lower extremity was ligated; *B*, that both lower extremities were ligated; *C* indicates the point at which the ligature was applied; *D*, the point at which it was removed. The metabolism level is indicated by 0.

Body surface furnishes a biometric measurement which indicates, with approximate accuracy, the probable amount of active protoplasmic tissue in different persons. Body surface is a difficult surface to measure, involving the use of complicated formulas. To date, however, it seems to be the most practical single prediction standard for adults.

Talbot [15] believes that the total metabolism for height will be the best single standard for children from 2 weeks to 12 years of age,

15. Talbot, F. B.: Basal Metabolism of Children, Physiol. Rev. **5**:477 (Oct.) 1925.

although he advises the use of all available standards in order to obtain a complete picture.

All standards are used for comparison in our department, but we find the Pirquet "sitting-height" standard the best single standard. Pirquet, like Rubner, found a surface proportional to the nutritional needs of the body, but instead of using the outer surface, he looked for another surface which would be simpler to measure and which would also approximate the development and growth of the organism. In studying

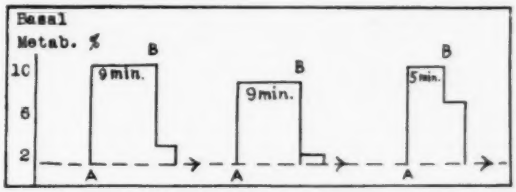

Chart 2.—Effect on basal metabolism of the application of ice to extremity not ligated. The first curve represents the experiments of Topper; the second, those of Mulier; the third, those of Helmreich. *A* indicates the point at which ice was applied; *B* indicates the removal of the ice. The metabolism level is indicated by 2.

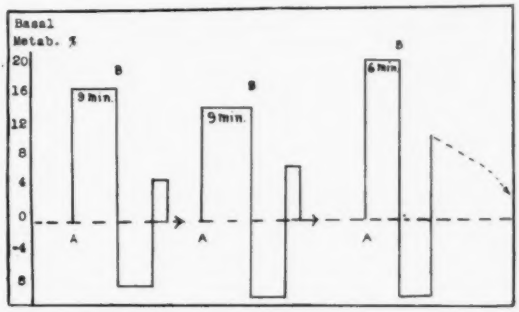

Chart 3.—Effect on basal metabolism of application of ice to ligated extremity. The first curve represents the experiments of Topper; the second, those of Mulier; the third, those of Helmreich. *A* indicates the point at which the ligature and the ice were applied; *B*, the point at which they were removed. The metabolism level is indicated by 0.

the relationship existing between the heart, pulse rate and body weight, he discovered that the sitting height (height of the trunk) stands in close relationship to the cube root of the body weight, and that this relationship remains constant throughout life. The sitting height is easily measured with the simplest apparatus, and its application requires only

squaring instead of squaring and cubing, as do all other formulas for body surface. The minimal or basal metabolism corresponds to about three decinemsiqua, or translated into calories, 0.2 calory times si^2 equals basal metabolism. We find that this simple formula gives us the best single standard for basal metabolism, and it applies to adults as well as to children.

SUMMARY

In a series of experiments performed on ourselves, we found that when the lower extremities are cut off from the general circulation by ligation, the basal metabolism is decreased by an amount which roughly corresponds to the mass thus occluded and not to the surface area (table 1). When the ligature was removed, the level of the basal metabolism rose to normal.

If basal metabolism were dependent on body surface, the ligation of large parts of the body mass should not have any effect on the level of metabolism so long as the surface remains intact. That the surface remained intact in this case was proved by the fact that we reacted to tactile, pain and thermal stimuli applied to the ligated part (charts 2 and 3).

This work was a repetition of work originally done by Helmreich, and our observations are in accord with his observations.

Helmreich concludes from his experiment that basal metabolism is independent of body surface, but rather depends on the amount of active protoplasmic tissue.

It is not the purpose in this paper to discuss how far the results of our experiment and those of Helmreich's prove or disprove his conclusions. We realize that the problem is complex, and that further studies are necessary in order to decide the relation between basal metabolism and the active protoplasmic mass.

BASAL METABOLISM

I. CORRELATION OF BASAL METABOLIC RATE AND BASAL PULSE RATE

JAMES H. SMITH, M.D.
RICHMOND, VA.

In 1920, Sturgis and Tompkins [1] reviewed the literature dealing with the relation between basal metabolism and resting pulse rate, and reported the results of their own study with special reference to hyperthyroidism. They found that a general parallelism existed between the basal metabolism and the pulse rate. In all but 16 per cent of 154 patients with hyperthyroidism, there was a tachycardia of 90 or more to the minute associated with a basal metabolism of + 15 per cent or more. On the other hand, they found that during complete rest a pulse rate below 90 per minute is seldom found and that below 80 per minute is rarely associated with an increase in metabolism.

Minot and Means [2] found that the amount of elevation in the pulse rate for a given elevation in the metabolic rate is essentially the same in hyperthyroidism and in chronic leukemia, and they infer that in both diseases the tachycardia is chiefly the result of an increased metabolic rate. Thus, incidentally, their study tended to confirm the conclusions of Sturgis and Tompkins with reference to metabolism and pulse rates that were above normal.

In 1923 and again in 1926, the basal metabolism-basal pulse ratio was plotted in two series of unselected cases, with results similar to those of Sturgis and Tompkins. They are presented in charts 1 and 2 dated with their respective years. The fields are divided at 90 on the pulse rate scale (horizontal) and at + 20 on the metabolic rate scale (vertical). The determinations of the metabolic rate are liable not only to the possibilities of error inherent in all methods of indirect calorimetry, but to an additional possibility of error of 1 per cent plus or minus involved in calculations by a logarithmic chart.[3]

The two charts here presented were plotted with reference to the correlation of metabolism and pulse rates in cases of hyperthyroidism, and the conclusions were in full accord with those already quoted from

---

1. Sturgis, C. C., and Tompkins, E. H.: A Study of the Correlation of the Basal Metabolism and Pulse Rate in Patients with Hyperthyroidism, Arch. Int. Med. **26**:467 (Oct.) 1920.

2. Minot, G. R., and Means, J. H.: The Metabolism-Pulse Ratio in Exophthalmic Goiter and in Leukemia, Arch. Int. Med. **33**:576 (May) 1924.

3. Smith, J. H., and Smith, M. C.: Boston M. & S. J. **186**:641 (May) 1922.

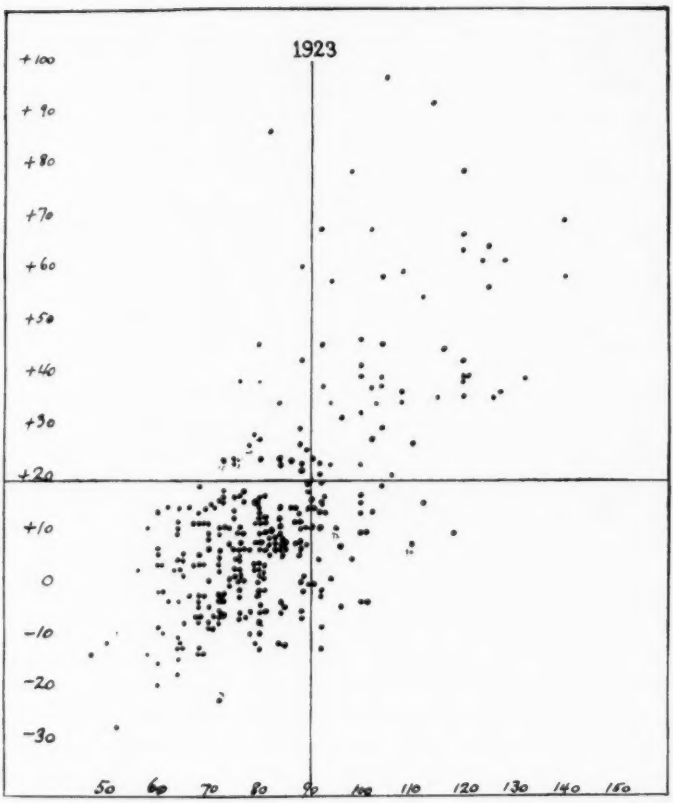

Chart 1.—Basal metabolism—basal pulse ratio in a series of unselected cases in 1923.

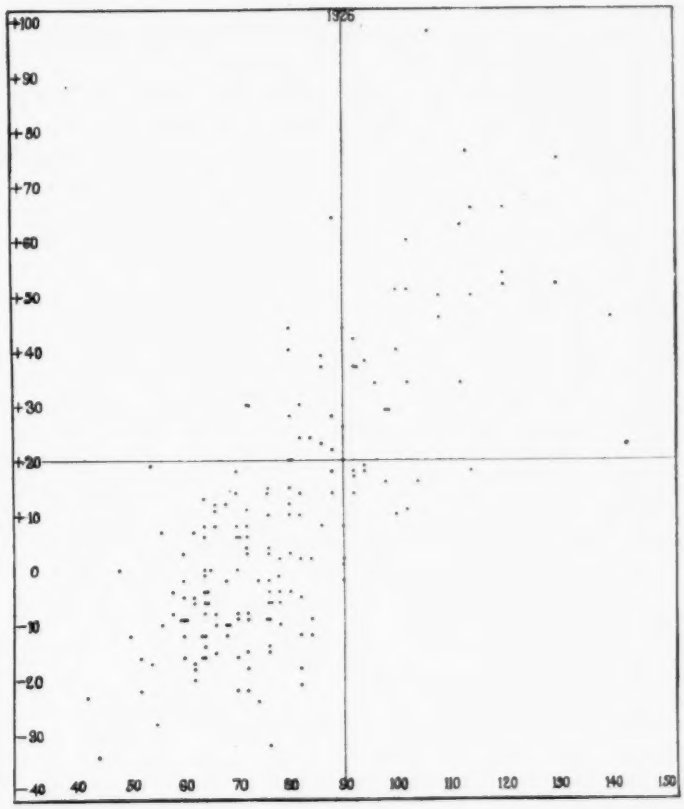

Chart 2.—Basal metabolism—basal pulse ratio in a series of unselected cases in 1926.

Sturgis and Tompkins. The charts are shown, however, with the special object of emphasizing the value of the basal pulse rate as a control of the acceptability of metabolic determinations and as tending to justify the valuation put on the pulse rate in my next paper.

It is obvious that the number of patients with a basal pulse rate of over 90 and a metabolic rate under + 20 (southeast field in charts) is not of great importance, as the chances of error in normal or in low metabolic readings are not so great as in those above normal, and it is more usual to find tachycardia due to causes other than hyperthyroidism than to find hyperthyroidism in a patient with a normal or low pulse rate. On the other hand, a basal metabolic rate of + 20 or more with a basal pulse rate under 90 (northwest field) gives rise to some suspicion of the accuracy of the metabolic study, and often repetition of the test will give a lower reading, as it did in certain of the cases plotted in the northwest field of each chart.

DETERMINATION OF CARDIAC HYPERTROPHY BY ROENTGEN-RAY METHODS*

J. A. E. EYSTER, M.D.
MADISON, WIS.

The differentiation of the enlarged heart from the heart of normal size is the most important single factor in determining the presence or absence of organic heart disease. With the exception of mitral stenosis and atrophic myocarditis, all but the rarest types of organic heart disease lead to hypertrophy of the ventricles. Except in rare instances, the left ventricle is most affected in the types with which the physician has to deal. This chamber is most affected in double mitral disease, in aortic disease, in adherent pericardium, in arterial hypertension and in myocardial degeneration associated with syphilitic or other types of aortitis and arterial injury. The greatly hypertrophied heart in advanced organic disease is easily recognized by the usual methods of physical examination, but there is need for more accurate differentiation of the hearts that are less abnormal and associated with an earlier stage in the pathologic process. This is the period when there is a possibility of retarding the advance of the condition, or, what is equally important, when persons with normal hearts who suspect or who have been told that they have organic heart disease can be given reassurance.

Studies in most of the lower animals (Hatai,[1] Pearce, Van Allen and Brown,[2] Josephs,[3] Herrmann[4]) and in man (Boyd,[5], Thoma,[6] Müller,[7] Beneke,[8] Vierordt,[9] Kress,[10] Greenwood and Brown[11]) have

* From the Department of Physiology, University of Wisconsin.

1. Hatai, S.: On the Influence of Exercise on the Growth of Organs in the Albino Rat, Anat. Record **9**:647, 1915.

2. Brown, W. H.; Pearce, Louise, and Van Allen, C. M.: The Relation Between Body and Organ Weights in the Rabbit, J. Exper. Med. **44**:635, 1926.

3. Josephs, D. R.: The Ratio Between the Heart Weight and Body Weight in Various Animals, J. Exper. Med. **10**:521, 1908.

4. Herrmann, G. R.: Experimental Heart Disease, Am. Heart. J. **1**:485, 1926.

5. Boyd: Tables of the Weights of the Human Body and Internal Organs, Philosophical Tr. Royal Soc. London **151**:241, 1861.

6. Thoma: Untersuchungen über die Grösse und des Gewicht der anatomische Bestandtheile, Leipzig, 1882.

7. Müller, W.: Die Massenverhältnisse des menschlichen Herzens, Hamburg and Leipzig, 1883.

8. Beneke, F. W.: Die anatomischen Grundlagen der Constitutions, Anomalien des Menschen, 1878.

9. Vierordt: Daten und Tabellen, 1906.

10. Kress, E.: Ueber Organgewicht bei Kindern, Dissertation, Munich, 1902.

11. Greenwood and Brown: A Study of the Weight, Variability and Correlation of the Human Viscera, Biometrika. **9**:473, 1913.

shown that the weight of the heart is more closely related to the size of the body than any other organ with the exception, perhaps of the brain. It is impossible, of course, to weigh the heart of a living being, and one is restricted to an estimation of its size or volume. This, however, is not a question merely of the muscle mass but of the amount of blood contained in the chambers of the organ, and this in turn varies with the particular phase of the cardiac cycle. Direct determination in the experimental animal (dog) indicates that the volume of blood in the heart in diastole is slightly less than that of the muscle of the heart (Bardeen[12]). Variations in the diastolic size of the heart may readily result from variations in the degree of cardiac filling, and it is possible to suppose that determination of the diastolic size in a given subject would be so variable as not to give a valid index of the true muscle mass. The modern conception of this phase of cardiodynamics is that the filling is primarily determined by systemic venous pressure, and there is reason to believe that under conditions of body rest it is fairly constant, although considerable increase may occur in muscular activity. The filling pressure even in cases of chronic heart disease is not increased unless decompensation occurs.[13] Unless the changes in the heart rate are marked, they do not greatly alter the diastolic size (Meek[14] and Hodges and Eyster[15]). The diastolic volume thus appears to be fairly constant in the same patient at different times when he is not in a state of muscular activity, and this conclusion is confirmed when repeated estimates are made on the same subject by roentgen-ray methods (Eyster and Evans,[16] and Eyster, Meek and Hodges[17]). Assuming then that the mass of blood in the heart in diastole is a fairly constant factor under controlled conditions, variations in the heart volume should correspond closely to variations in the muscle mass. In valvular incompetence the increased ventricular output, however, makes probable the assumption of increased

12. Bardeen, C. R.: Determination of the Size of the Heart by Means of the X-Rays. Am. J. Anat. **23**:423, 1918.

13. Eyster, J. A. E.: Venous Pressure and Its Clinical Applications, Physiol. Rev. **6**:281, 1926.

14. Meek, W. J.: The Effect of Changes in Pulse Rate on Diastolic Heart Size, Am. J. Physiol. **70**:385, 1924.

15. Hodges, P. C., and Eyster, J. A. E.: Estimation of Cardiac Area in Man, Am. J. Roentgenol. **12**:252, 1924.

16. Eyster, J. A. E., and Evans, J. S.: Value of the X-Ray in Diagnosis of Chronic Valvular Heart Disease, Tr. A. Am. Phys., 1923.

17. Eyster, J. A. E.; Meek, W. J., and Hodges, F. J.: Cardiac Changes Subsequent to Experimental Aortic Lesions, Arch. Int. Med. **39**:536 (April) 1927.

diastolic filling, and a part of the enlargement that is found in such cases must be accredited to the increased mass of blood within the heart.

An estimation of the cardiac size in man can be made only indirectly by the projection of one or more of the surface planes of the heart. Two general methods have been employed for this purpose: topographic percussion and the roentgen-ray projection. It is generally agreed that the latter is more objective and accurate. In order to avoid the distortion and enlargement of the silhouette in roentgen-ray projection, two methods have been employed: teleroentgenography and orthodiagraphy. In the former the film is placed as close to the heart as possible, and the source of the divergent roentgen rays, the target of the tube, is placed sufficiently far away to give approximately parallel rays. The usual working distance is 2 meters or approximately 7 feet, and under these conditions the enlargement of the silhouette as compared to the plane of the heart is approximately 3 per cent in linear dimensions. In orthodiagraphy, the principle of orthographic projection first applied by Moritz,[18] in which only the central or incident bundle of rays is used to form the projection, a silhouette of the same size as the plane of the object casting the shadow is secured by parallel ray projection. If the heart were a sphere, its volume could be calculated from the area of its projection in any plane.[19] This, however, is not the case, and the estimation of volume from one plane surface can be only an approximation. Theoretically, if projections of plane surface were obtained from a number of different views, the heart as a solid body could be reconstructed by orthographic projection, and its volume could thus be accurately determined, but practically, such reconstruction is difficult or impossible in man due to the interference of other structures with the shadow cast by the heart; structures such as the sternum, vertebral column, diaphragm and liver and by the great vessels at the base of the heart. Bardeen,[12] however, has shown by direct determination of the volume of the heart in cadavers that a fair approximation can be obtained from a single plane (the frontal), and Skavlem[20] has confirmed this on the dog.[21] From

18. Moritz, F.: Eine Methode um beim Röntgenverfahren aus dem Schattenbilde eines Gegenstandes dessen wahre Grösse zu Armitteln (Orthodiagraphie) und die exacte Bestimmung des Herzgrösse nach diesem Verfahren, München. Med. Wchnschr. **47**:992, 1900.

19. Volume = Plane area$^{3/2}$. $\frac{4}{3\sqrt{\pi}}$

20. Skavlem, J. H.: Estimation of Cardiac Volume in the Living Animal by Means of the Teleroentgenogram, Am. J. Physiol. **61**:501, 1922.

21. The formula for the human heart is, volume = 0.53 $A^{3/2}$ and for the dog's heart, volume = 0.44 $A^{3/2}$ when A equals the area of the silhouette of the frontal plane.

the standpoint of the clinical goal of separation of the hypertrophied from the normal heart such determination of volume is not essential if some other measurement or system of measurements is sufficient to ensure this separation. The real criterion of the value of any method of cardiac mensuration is its effectiveness in arriving at this differentiation.

REVIEW OF LITERATURE

Since the time of Moritz's first publication, numerous workers have attempted to establish normal standards for measurements applied to the silhouette of the frontal plane obtained by orthodiagraphy or teleroentgenography. Moritz [22] proposed a rather complicated system of vertical, longitudinal and transverse diameter measurements, and these were applied, with the addition of surface area of the silhouette by Dietlen,[23] in a large series of normal subjects. Other more or less extensive studies in normal subjects have been made by Groedel,[24] Clayton and Merrill,[25] Otten,[26] Williamson,[27] Shattuck,[28], Bardeen,[12] Haudek,[29] Bertnard Smith,[30] H. E. Smith and Bloedern [31] and Cohn.[32] In these studies efforts have been made to relate the measurements found with certain body measurements, especially in height and weight, and with age, sex and body conformation. There has also been a tendency to reduce the number of silhouette measurements and to emphasize the value of two, the area of the frontal plane and the greatest transverse diameter of the silhouette of the frontal plane. The former appears to have the advantage of combining the elements of the various

22. Moritz, F.: Ueber orthodiagraphische untersuchungen am Herzen, München. Med. Wchnschr. **49**:1, 1902.

23. Dietlen: Ueber Grösse und Lage des normalen Herzens und ihre Abhängigkeit von physiologischen Bedingungen, Deutsches Arch. f. klin. Med. **88**:54, 1907.

24. Groedel, F. M.: Die Röntgendiagnostik der Herz und gefasser Erkrankungen, Berlin, 1912.

25. Clayton, T. A., and Merrill, W. H.: Orthodiagraphy in the Study of the Heart and Great Vessels, Am. J. M. Sc. **138**:549, 1909.

26. Otten, M.: Die Bedeutung der Orthodiagraphie für die Erkennung des beginnenden Herzweiterung, Deutsches Arch. f. klin. Med. **105**:370, 1911.

27. Williamson, C. S.: The Effects of Exercise on the Normal and Pathological Heart, Am. J. M. Sc. **138**: 549, 1909.

28. Shattuck, G. C.: How Can We Detect Slight Enlargement of the Heart? Boston M. S. J. **174**:385, 1916.

29. Haudek, M.: Röntgenologie—Eine Revision der Methodik der röntgenologischen Herzgrossenbeurteilung, Jahreskurse fur ärtzliche Fortbildung, 1918.

30. Smith, B.: Teleroentgen Measurements of the Hearts of Normal Soldiers, Arch. Int. Med. **25**:522 (May) 1920.

31. Smith, H. E., and Bloedern, W. A.: U. S. Nav. M. Bull. **16**: 219, 1922.

32. Cohn, A. E.: An Investigation of the Size of the Heart in Soldiers by the Teleroentgen Method, Arch. Int. Med. **25**:499 (May) 1920.

diameter measurements and to be less subject to variation from minor influences, but it has the disadvantage that it requires arbitrary completion of the upper border of the cardiac shadow when it merges with the great vessels and of the lower border when it is contiguous with the diaphragm. This difficulty is much greater in teleroentgenography than in orthodiagraphy, and it is impossible to make satisfactory measurements in many teleroentgenograms in subjects with a short thorax and a high diaphragm. A much more accurate completion of the lower border can be obtained by orthodiagraphy, because of the possibility of separating two shadows of approximately equal density (heart and diaphragm) by taking advantage of their differences in movement (Eyster [33]). Completion of the border contiguous to the greater vessels is also more accurate when done orthodiagraphically, because of the possibility of the location of the junction of the right auricle and the vena cava on the right contour and of the left auricle and left ventricle on the left contour of the heart. The greatest transverse diameter of the silhouette of the frontal plane has the advantage of being the most objective and definite measurement that can be applied to this silhouette. It, however, appears to be more variable as a result of minor influences such as the extent of the stomach filling and the phase of respiration. All measurements of the silhouette of the heart, so far as I know, have been confined to the frontal plane, although observations on the extent of the retrocardiac space (space between the posterior border of the heart and the vertebral column) in the lateral plane have been recorded by Vaquet and Bordet [34] and by Eyster and Evans [16] and Eyster.[33]

P. C. Hodges and Eyster [15] and F. J. Hodges and Eyster [35] published prediction tables for the size of the normal heart based on surface area and transverse diameter of the orthodiagraphic silhouette of the frontal plane in which the variables of age, height and weight were subjected to mathematical analysis. The subjects represented a group of normal persons selected after careful clinical examination. By this method it was possible to evaluate the different variables and to give them proper weight in the regression equation on which the prediction tables were based, and thus to assure, it was believed, a more accurate prediction than that found in tables previously published. The true evaluation, however, of a method such as this is its ability to separate

33. Eyster, J. A. E.: The Size of the Heart in the Normal and in Organic Heart Disease, Radiology, 1927.

34. Vaquez, H., and Bordet, E.: The Heart and the Aorta, English translation by J. A. Honeji, New Haven, 1920.

35. Hodges, F. J., and Eyster, J. A. E.: Estimation of Transverse Cardiac Diameter in Man, Arch. Int. Med. **37**:707 (May) 1926.

the normal from the enlarged heart, and in order to test this I applied the method in a study of 424 cases of normal and chronic heart disease.[33] It was found that subjects with organic heart disease of types that were known to be associated with hypertrophy were differentiated with a degree of accuracy that would lead to the conclusion that the method was of distinct clinical importance. In cases of mitral and aortic disease, selected as characteristic of the earlier stages of the lesion before signs or symptoms of cardiac failure had occurred, a distribution above the upper normal range of 84 per cent of all cases was shown. Ninety-four per cent were more than 10 per cent above the predicted normal area, while in the normal series of cases only 9 per cent of all cases exceeded the prediction by more than 10 per cent. Similar but less marked separation could be made on the basis of the greatest transverse diameter.

METHODS

The present study is concerned with an attempt to evaluate the introduction of other measurements of orthodiagraphic silhouettes and of other body measurements in relation to the prediction of the size of the normal heart and the separation of normal and hypertrophic hearts. The measurements of the silhouettes studied were the area and greatest transverse diameter of the silhouette of the lateral plane combined with similar measurements from the frontal plane. The additional body measurements introduced were the anteroposterior and lateral diameters and the girth of the thorax (made at the third intercostal space). A new series of 100 carefully selected normal persons was studied and compared with 100 patients with organic heart disease; the latter group comprised 55 cases of mitral stenosis and regurgitation, 25 cases of aortic regurgitation, 10 cases of aortic and mitral disease, 15 cases of hypertension with clinical signs of cardiac hypertrophy and 5 cases with clinical signs of adherent pericardium. In all of these cases the compensation of the heart was good, and the history did not suggest cardiac failure. The data from the normal series were submitted to mathematical analysis, and regression equations were determined for prediction, the new silhouette and body measurements being used. The data, including thoracic measurements, are restricted to fifty cases in each group. In the mathematical treatment of these data it became evident that the best prediction combination of the four cardiac measurements, the areas of the frontal and lateral planes and the transverse diameters of the frontal and lateral planes, was the sum of the two transverse diameters, and that the addition of the areas contributed too little to justify their inclusion in the final formula.

New formulas were also developed for the area of the frontal plane and transverse diameter, including the thoracic measurements in addition to age, height and weight as variables.

With the new prediction tables available, the next step was to test the degree of separation of the normal and pathologic by plotting the results of each group on distribution curves. In these curves, the results in cases corresponding with the prediction are plotted as showing zero variation, and those of other cases are plotted according to whether they vary in percentage from the prediction above (+) or below (—). The extent of overlapping of the normal and pathologic, the range between an arbitrary percentage variation from the predicted (± 10 per cent) and the percentage of pathologic cases exceeding the upper normal range are shown. Three additional simple ratios available from the data are included; these concern the relation between the transverse diameter and the area of the silhouette of the frontal plane and the thoracic measurements.

MATHEMATICAL TREATMENT

An attempt to discuss the statistical theory in detail on which the mathematical treatment of the present material is based would be out of place in the present communication, and it must suffice to refer to the writings of Thorndike,[36] Pearson,[37] Yule[38] and Hull,[39] to its application to biologic study by Harris and Benedict[40] and to its previous application to cardiac mensuration by Hodges and Eyster.[41]

The method depends on obtaining partial and multiple coefficients of correlation and in giving to each variable a weight that will produce the highest degree of correlation between the variables and the criterion. In the first study, that in which measurements from the silhouettes of both the frontal and the lateral planes were employed, there were four criteria: the area of the frontal plane, the transverse diameter of the frontal plane, the area of the lateral plane and the transverse diameter of the lateral plane. The variables were age, height or stature, and weight. In the second mathematical treatment of the material, thoracic measurements were also introduced as variables. In addition to the four basic measurements of the heart, treated separately, various combinations were tested as follows: the sum of the areas of the frontal and lateral planes, the sum of the transverse diameters of the frontal and lateral planes, the product of the transverse diameter of the frontal plane by the area of the lateral plane and the product of the transverse diameter of the lateral plane by the area of the frontal plane. All possible intercoefficients of correlation were first com-

36. Thorndike, E. L.: An Introduction to the Theory of Mental and Social Measurements, Columbia University Press.

37. Pearson, Karl: Tables for Statisticians and Biometricians, Cambridge University Press, 1914.

38. Yule, G. U.: An Introduction to the Theory of Statistics, London, Charles Griffin, 1919.

39. Hull, C. L.: Prediction Formulae for Teams of Aptitude Tests, Applied Psychology **7**: 277, 1923.

40. Harris, J. A., and Benedict, F. G.: A biometric Study of Basal Metabolism in Man, Carnegie Institute, Washington, 1919.

41. Hodges, P. C., and Eyster, J. A. E. (footnote 15) and Eyster, J. A. E. (footnote 33).

puted as well as the mean and standard deviations, the correlating machine devised by Hull being used and checked to absolute accuracy. The formula used for obtaining the simple coefficients of correlation was:

$$r = \frac{M_1X_2 - M_1XM_2}{\sqrt{M^2_1 - (M_1)^2}\ \sqrt{M^2_2 - (M_2)^2}}$$

The multiple coefficients of correlation were obtained by the formula.

$$R_{o\ 1,\ 2,\ 3} = \frac{W_1P_{o1} + W_2P_{o2} + W_3P_{o3}}{P_{oo}}$$

In table 1 is given the multiple coefficients of correlation for the various combinations of the heart and body measurements. These figures express the extent of correlation or agreement between these measurements and give an

TABLE 1.—*Multiple Coefficients of Correlation for Various Combinations of Heart and Body Measurements*

Heart Measurements	Age, Height, Weight	Age, Height, Weight and Thoracic Measurements
Area of frontal plane	0.547	0.575
Transverse diameter of frontal plane	0.693	0.681
Area of lateral plane	0.454	0.444
Transverse diameter of lateral plane	0.499	0.598
Sum of areas of lateral and frontal planes	0.631	0.635
Sum of transverse diameters of lateral and frontal planes	0.700	0.734
Area of frontal and transverse diameter of lateral plane	0.616	0.622
Transverse diameter of frontal plane and area of lateral plane	0.654	0.671

index of the accuracy of prediction that it is possible to make. The prediction formulas developed were as follows:

1. Formula for the sum of the transverse diameters of the frontal and lateral planes based on age, height and weight:

$X_o = 0.28542 \times \text{age} - 0.489355 \times \text{height} + 1.34498 \times \text{weight} + 185.84.$

2. Formula for the sum of the transverse diameters of the frontal and lateral planes based on age, height, weight and thoracic measurements.

$X_o = -0.19175 \times \text{age} - 1.17373 \times \text{height} + 1.10799 \times \text{weight} - 0.07063 \times \text{anteroposterior diameter} + 0.07835 \times \text{lateral diameter} + 0.75981 \times \text{girth} + 260.306.$

3. Formula for the area of the frontal plane based on age, height, weight and thoracic measurements.

$X_o = -0.61315 \times \text{age} + 0.050378 \times \text{height} + 0.578655 \times \text{weight} - 0.18051 \times \text{anteroposterior diameter} + 0.160057 \times \text{lateral diameter} - 0.2876 \times \text{girth} + 81.18.$

4. Formula for the transverse diameter of the frontal plane based on age, height, weight and thoracic measurements.

$X_o = -0.05932 \times \text{age} - 0.914298 \times \text{height} + 0.959396 \times \text{weight} - 0.20951 \times \text{anteroposterior diameter} + 0.0256 \times \text{lateral diameter} + 0.49855 \times \text{girth} + 208.2.$

Chart 1.—Distribution of measurements from frontal and lateral orthodiagrams in normal cases and in cases of organic heart disease.

RESULTS OF STUDY

The results of this study are given in the form of distribution curves in charts 1 and 2. With the exception of the four last columns in chart 2 (from 17 to 20 inclusive), the results of each are charted in regard to their variation in percentage from the predicted. In columns 1 and 2 and in 7 and 8, concerned with the area and transverse diameter of the frontal plane respectively, prediction was based on the arithmetical means of the normal series. These means were 112

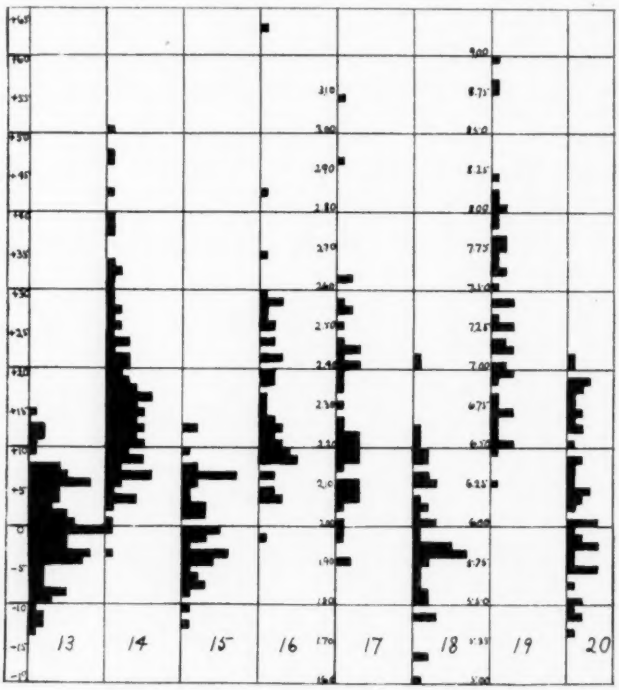

Chart 2.—Distribution of measurements from frontal and lateral orthodiagrams in normal cases and in cases of organic heart disease.

sq. cm. in the area of the frontal plane and 124 mm. in the transverse diameter of the frontal plane. In all the other columns (except columns 17 to 20), prediction was based on one of the formulas developed in this or in previous work (Hodges and Eyster[41]). In the last four columns of chart 2, the results are charted as actual measurements.

In columns 1 to 6 inclusive, the areas of the frontal plane are considered. Column 1 represents the distribution of 100 normal subjects in which the areas of the frontal plane are charted according to their

variation from the arithmetical mean of the group (112 sq. cm.). Column 2 represents the distribution of 100 cases of organic heart disease from the normal mean. Columns 3 and 4 represent similar considerations of the normal and abnormal groups in which prediction was based on the formula, age, height and weight being used as variables (Hodges and Eyster [15]), and columns 5 and 6 comprise fifty cases in each group in which the additional variables of thoracic measurements were introduced and predicted according to formula 3. Columns from 7 to 12, inclusive, represent an exactly similar series in which the determination of the transverse diameter of the frontal plane was made. Column 7 represents the normal series based on the arithmetical mean (124 mm.), and column 8 the abnormal group similarly predicted. Column 9 represents the normal group in which prediction was made by the formula, age, height and weight previously published (Hodges and Eyster [35]) being employed, column 10 similar treatment of the abnormal group, and columns 11 and 12 groups of fifty cases each from the normal and abnormal groups, thoracic measurements being used as additional variables in the prediction according to formula 4.

The first four columns of chart 2 represent the application of the additional cardiac measurements from the silhouette of the lateral plane. Consideration of the area and transverse diameter of the lateral plane alone and in combination with measurements of the frontal plane indicated that the best prediction would be obtained by employing the sum of the two diameters, the frontal and the lateral (table 1). Inclusion of area measurements complicated the procedure without improving it. Accurate delineation of the contour in its upper and lower boundaries is more difficult in the lateral than in the frontal plane owing to the greater density of the shadows cast by the diaphragm and the interposition of the hila of the lungs. The anterior and the posterior contour, so long as the latter is clear from the shadow of the spinal column, are, however, readily obtained with accurate measurement of the greatest transverse diameter. Formulas were developed to predict the sum of the two transverse diameters, age, height and weight being used as variables (formula 1) and the introduction of thoracic measurements as additional variables (formula 2). Column 13 (chart 2) shows the distribution from the predicted of the same group of 100 normal cases, and column 14 shows the same group of 100 pathologic cases previously employed in the other types of measurement, height and weight being used as variables (formula 1). Columns 15 and 16 show results in fifty cases in each of the normal and pathologic series in which thoracic measurements were available and which were predicted by formula 2.

Columns 17 to 20, inclusive, represent simple ratios between the transverse diameter of the silhouette of the frontal plane and

the transverse diameter and girth of the thorax, respectively. As there is no normal prediction in these, they are plotted, not as variations in percentage, but as the actual ratio. In column 17, the results from the ratio $\frac{\text{Transverse Diameter of the Thorax}}{\text{Frontal Transverse Diameter of the Heart}}$ of fifty normal subjects are plotted, and column 18 represents the same from fifty subjects with organic heart disease. Column 19 records the ratio $\frac{\text{Girth of the Thorax}}{\text{Frontal Transverse Diameter of the Heart}}$ in the same series of normal subjects and column 20 in the same series of pathologic cases.

COMMENT

The real criterion for the value of any method applied in clinical diagnosis is its ability to separate the normal and pathologic cases. Considered in this light it appears obvious that the area and transverse diameter of the frontal plane, predicted from age, height and weight, are of definite value, and that little if anything is gained by the introduction of other cardiac or body measurements (thoracic). Measurements from the silhouette of the lateral plane appear to improve slightly the prediction in normal cases (comparison of column 13 with columns 3 and 9), but the separation from the pathologic is less. The probable reason for this is that the true measurement of the transverse diameter of the silhouette of the lateral plane is not obtained in enlargement of the left ventricle, because the posterior cardiac contour is displaced dorsally and fuses with the shadow of the spinal column resulting in an obliteration of the retrocardiac space. This measurement, which it is possible to make accurately in the normal subject, thus is probably underestimated in most of the pathologic cases.

Three ratios between measurements from the silhouette of the frontal plane and thoracic measurements have also been considered. The first of these, the ratio between the greatest transverse diameter of the heart and the transverse diameter of the thorax (columns 18 and 19, chart 2) has been advocated by Kreufuchs [42] and by Danzer.[43] It is the method for attempting to distinguish hypertrophied hearts which has been most widely used in this country. According to Danzer, the width of the heart forms from 39 to 50 per cent of the width of the thorax in normal subjects. If the diameter of the heart is more than half the diameter of the thorax, the possibility of hypertrophy should be considered, and if the percentage of the diameter of the heart rises to 53 per cent or more, hypertrophy is definitely present. In hearts of the "drop" type, of small initial transverse diameter, consider-

42. Kreufuchs: Eine neues Verfahren des Herzmessung, München Med. Wchnshcr. **59:** 1030, 1912.

43. Danzer, C. S.: The Cardio-Thoracic Ratio; an Index of Cardiac Enlargement, Am. J. M. Sc. **157:**513, 1919.

able hypertrophy may develop, however, without the ratio exceeding the normal range, and Danzer's final conclusion is that if the cardiothoracic ratio exceeds the normal range, hypertrophy is constituted; if not the possibility of hypertrophy cannot be ruled out. It is evident from a consideration of this method in the present series of cases that it has little clinical value. It is, in fact, little better than assuming an average transverse diameter as the basis for prediction, and it gives a distinctly poorer prediction than any of the methods using the area of the frontal plane, including the one based on average values. Distinctly better separation of normal and hypertrophied hearts is obtained by employing the thoracic girth in the ratio instead of the transverse diameter of the thorax (columns 19 and 20, chart 2), and an even better ratio is that between the cardiac area of the frontal plane and the thoracic girth (table 2). The latter, however, involves measurement of the area of the plane and does not have any advantage over the prediction based on age, height and weight. It does, however, emphasize the fact that the area of the silhouette of the frontal plane is a more valuable measurement than the transverse diameter and more neatly approximates a determination of the true size of the heart. In the present series of normal subjects, the transverse diameter of the heart was less than half the transverse diameter of the thorax in 94 per cent, but this was also true in 38 per cent of the pathologic cases, and only 42 per cent of the latter equaled or exceeded Danzer's upper range of 52 per cent.

In order to show more clearly the value of the different methods considered, certain points are included in table 2. The first column gives the type of measurement employed, and the succeeding four columns the percentage of cases lying between $\pm$ 10 and above $+$ 10 per cent in the normal and pathologic series. The sixth column gives the percentage of the pathologic cases that exceed the upper range of the normal. In an effort to evaluate the separation of the normal and pathologic cases, the seventh column is included in which the figures represent the percentge above $+$ 10 per cent in the normal subtracted from the percentage above $+$ 10 per cent in the pathologic as a measure of the extent of overlapping beyond what may be considered as a fair upper normal variation. To give a final figure representing the order of value of the different methods, the eighth column gives the sum of the two preceding columns. It is obvious that the determination of the area of the frontal plane is the most important single cardiac measurement, and that little if anything is gained by inclusion of other cardiac or of body measurements in addition to those of height and weight. In a preceding paper [35] it has been pointed out that possibly a gain would be made in accuracy of prediction of the size of the heart by including other

TABLE 2.—*Comparison of Different Methods for Predicting Orthodiagraphic Measurements of the Heart*

Type of Measurement	Normal		Pathologic Cases			Percentage Above +10 in Normal Subjects Subtracted from Percentage Above +10 in Pathologic Cases	Addition of Last Two Columns	Order of Value	Columns in Charts 1 and 2
	Between ±10%	Above +10%	Between ±10%	Above +10%	Above Upper Normal Range				
Area of frontal plane, based on average; no prediction	66	19	17	82	43	63	106	9	1 and 2
Area of frontal plane; prediction based on age, height, weight	78	6	9	91	78	85	163	1	3 and 4
Area of frontal plane; prediction based on age, height, weight and thoracic measurements	80	6	12	88	66	82	148	2	5 and 6
Transverse diameter of frontal plane; no prediction; based on average	70	17	39	60	17	43	60	11	7 and 8
Transverse diameter of frontal plane; prediction based on age, height, weight	84	8	22	78	55	70	125	5	9 and 10
Transverse diameter of frontal plane; prediction based on age, height, weight and thoracic measurements	86	6	24	76	60	70	130	4	11 and 12
Sum of transverse diameters of frontal and lateral planes; prediction based on age, height, weight	89	6	27	73	49	67	116	7	13 and 14
Sum of transverse diameters of frontal and lateral planes; prediction based on age, height, weight and thoracic measurements	94	4	34	66	50	62	112	8	15 and 16
Transverse diameter of thorax									
Transverse diameter of heart	74*	10†	36	64†	26	54	80	10	17 and 18
Girth of thorax									
Transverse diameter of heart	78*	12†	28	72†	60	60	120	6	19 and 20
Girth of thorax									
Area of frontal plane	62*	20†	6	94†	62	74	136	3	

The asterisk indicates ± as referred to average and the dagger indicates below −10 per cent.

body measurements, but if so these should be such as would correlate more closely with the size of the heart than with the body measurements already employed. It was shown, for example, that sitting height correlates so closely with standing height that either may be employed but that there is no advantage in using both. It appears probable that a type of body measurement will not be found which correlates better with the size of the heart than height and weight, unless perhaps it is some other organ weight obviously impossible of clinical use. Inclusion of other measurements thus introduces complications without corresponding improvement in the accuracy of prediction.

Considerable criticism has been directed to the use of the area of the frontal plane because of the necessity of the arbitrary completion of portions of the cardiac contour, and it has been regarded as so inaccurate and subjective in nature as to lead to its rejection by certain recent workers (Deutsch and Kauf [44]). My rather long experience with this method has led to the conviction that it is accurate if measured from the orthodiagraphic tracing made by one with some experience in this type of work. Repeated determinations on the same person and comparison of orthodiagrams made by different observers confirm this view. On the other hand, it is most inaccurate when an attempt is made to apply it to many teleroentgenograms, and if used at all with them, it should be applied only in selected cases in which the heart lies relatively free from the diaphragmatic shadow. If one must work with teleroentgenograms, it is preferable to rely on the greatest transverse diameter which is accurately obtained and predicted according to the formula previously published (Hodges and Eyster [35]) or perhaps by employing the ratio of the thoracic girth as the present work suggests. Orthodiagraphy should be employed whenever possible, not only because it leads to more accurate mensuration, but because it also allows a fluoroscopic examination of the great vessels, and observation in the lateral and in the various oblique planes when desirable. In my opinion the roentgen ray is as valuable in the diagnosis of cardiovascular diseases as it is in gastro-enterology, and it is far more comprehensive in the information it supplies than any of the other adjuncts of clinical study.

CONCLUSIONS

1. A comparison of the area of the orthodiagram of the frontal plane with the predicted area using age, height and weight as variables affords the best separation so far employed in differentiating between normal and hypertrophic hearts.

---

44. Deutsch, F., and Kauf, E.: Heart and Athletics, English translation by L. M. Warfield, St. Louis, C. V. Mosby Company, 1927.

2. The introduction of other body (thoracic) and heart measurements from other planes results in little if any gain in accuracy.

3. The transverse diameter of the silhoutte of the frontal plane (orthodiagraphic or teleroentgenographic) similarly predicted or determined from the ratio $\frac{\text{Thoracic Girth}}{\text{Transverse Diameter of the Heart}}$ represents what appears to be the next most valuable method for differentiation.

ROENTGEN-RAY TREATMENT OF THE SPLEEN IN ASTHMA AND IN RELATED ALLERGIC DISEASES *

GEORGE L. WALDBOTT, M.D.
DETROIT

In 1920, Drey and Lossen [1] treated a patient who was afflicted simultaneously with leukemia and bronchial asthma by irradiation of the spleen with the roentgen ray; they noticed that the asthmatic condition improved appreciably. Similar reports of the recovery of asthmatic patients following irradiation administered to alleviate other ailments are given by Scott [2] and Schilling.[3] In 1925, Groedel [4] treated a number of asthmatic patients by irradiation of the spleen and was favorably impressed with the results. Others (Pohlmann,[5] Gallino and Terrada [6] and Moner [7] concurred in the optimistic opinions of the foregoing authors on the value of this form of therapy.

In this country, Gerber [8] introduced this procedure for the treatment of patients with asthma, and at the same time advocated exposure of the chest, the so-called direct method, which is based on the previous work of Klewitz,[9] Schilling [3] and others.

---

* From the Asthma Clinics of the Children's Hospital of Michigan and the North End Clinic.

1. Drey, L., and Lossen, H.: Beseitigung chronischen Bronchialasthmas durch Fernwirkung der Roentgenstrahlen bei Milzbestrahlung, Strahlentherapie **19**:1052, 1920.

2. Scott, G.: Method of Treating Asthma by Radiation, Brit. M. J. **1**:9 (June) 1926.

3. Schilling, T.: Günstige Beeinflussung der chronischen Bronchitis durch Roentgenstrahlen, Verhandl. d. Kong. f. inn. Med. **23**:463, 1906.

4. Groedel, F. M.: Die Roentgenbehandlung des Asthma bronchiale in Roentgenbehandlung Innerer Krankheiten, München, J. F. Lehman, 1922.

5. Pohlmann, C.: Milzbestrahlung bei Bronchialasthma, München. med. Wchnsehr. **72**:57 (Jan.) 1925.

6. Gallino, M. M., and Terrada, H. M.: Radio-Therapy of Asthma, Rev. Soc. de med. Torino **1**:132, 1925.

7. Moner, G.: La Radioterapia en le Esma Bronchial, Rev. Soc. Argentin. de Rad. y Electr. **1**:19, 1925.

8. Gerber, I.: Roentgen-Ray Treatment in Bronchial Asthma and Chronic Bronchitis, J. A. M. A. **85**:1026 (Oct. 3) 1925; Further Observations on the Roentgen-Ray Treatment of Bronchial Asthma and Allied Conditions, Radiology **9**:192 (Sept.) 1927.

9. Klewitz, D. F.: Roentgenbestrahlung bei Asthma bronchiale, München. med. Wchnschr. **69**:305 (March) 1922.

Cole and Ramirez,[10] who applied roentgen-ray treatment over the spleen and chest, do not, in their report, share the favorable impression of the aforementioned authors. An analysis of their records, however, indicates that the treatment of the spleen alone gave better results than the combined method. I [11] have previously given a detailed report of a case with the results of roentgen-ray treatment of the spleen, and I have subsequently published data obtained in ten cases.[12] The observations of the various authors [13] are recorded in table 1. Of 171 patients, 70.1 per cent were improved, 11.7 per cent failed to respond to the treatment, and the rest did not return for observation. In the reports of these cases, however, the clinical data are either lacking or incomplete, with the exception of the ones presented by Cole and Ramirez and those reported by me. Gasul,[14] who applied diathermy to the spleen, reports "excellent results."

TABLE 1.—*Results of Observations of Various Authors*

			Total Number of Patients	Results			
				Splendid	Good	None	Not Returned
Groedel	1922	Spleen	41	18	12	8	2
Pohlmann	1925	Spleen	42	..	40	2	..
Ramirez and Cole	1925	Spleen	8	..	4	4	..
Waldbott	1925	Spleen	10	..	6	2	2
Gallino and Terrada	1925	Spleen	26	12	10	2	2
Moner	1925	Spleen and lungs	22	7	..	1	5
Mueller	1926	Spleen and lungs	22	..	11	1	4
			171		126	20	15

In spite of these encouraging reports in the literature, roentgen-ray treatment of patients with asthma has not been universally adopted, a fact easily explained by the following: (1) the difficulty of gaining an unprejudiced view of the efficacy of any one remedy for asthma, (2) the insufficiency of experimental evidence on the use of this treatment and (3) the insufficient knowledge of a possible injurious action of the rays on the body.

10. Cole, L. G., and Ramirez, M. A.: Roentgen-Ray Therapy in Bronchial Asthma, Am. J. Roentgenol. **14**:322 (Oct.) 1925.

11. Waldbott, G. L.: Roentgen-Ray Treatment of the Spleen in Asthma, Arch. Int. Med. **36**:743 (Nov.) 1925.

12. Waldbott, G. L.: Treatment for Asthma and the Related Anaphylactic Diseases, J. Michigan M. Soc. **24**:588, 1925.

13. Mueller, A.: Roentgen-Ray Treatment of Bronchial Asthma, Med. Klin. **21**:1493 (Oct.) 1925.

14. Gasul, R.: Method of Treatment of Bronchial Asthma by Diathermy of Spleen, Strahlentherapie **21**:685, 1926.

"CURE" OF PATIENTS WITH ASTHMA

In reference to the first point, Kahn [15] has recently demonstrated that it is almost impossible to form an impartial opinion regarding the "cure" of asthma. The confusion encountered in analyzing the value of a therapeutic measure is explained by the large variety of factors which contribute both to the outbreak of an attack and to its subsidence. An apparent cure may be simply a result of the temporary absence of the exciting agents. Spontaneous remissions are often of long duration and are sometimes permanent.

EXPERIMENTAL EVIDENCE

In regard to the part which the spleen plays in the causation of anaphylaxis and allergy, reference has been made in a former publication [11] to experiments by Luckhardt, Becht, Carrel and Ingebrigsten, Hektoen, and Motohashi. These authors showed that the spleen is involved in the production of specific antibodies. Their work suggests that the removal of the spleen reduces the power of the animal to produce antibodies, whereas irradiation of the spleen increases the antibody titer of the blood. Doerr [16] and Schneider [17] have recently confirmed the theory that if roentgen-ray treatment is applied in proper doses, it prevents the production of anaphylaxis in animals. Although the anaphylactic experiment is not generally considered analogous to the mechanism of allergy (Coca [18]), the evidence obtained by these experiments suggests a close relationship of the spleen to the allergic phenomenon. Mayr and Moncorps [19] observed a marked reduction in the number of eosinophils in sensitized animals following the injection of extract from the spleen. When this procedure was used on human beings who showed allergic manifestations of the skin, the same result was encountered. Should these observations be confirmed, there would be reason to believe that hypofunction of the spleen results in hypereosinophilia and hyperfunction of the spleen in hypoeosinophilia or aneosinophilia. In view of the almost invariable association of eosinophilia with the phenomenon of allergy, these experiments suggest that the spleen is in some way concerned in the mechanism of asthma.

---

15. Kahn, M. H.: Present Status of Curability of Bronchial Asthma, Arch. Int. Med. **39**:621 (May) 1927.

16. Doerr, quoted by Schneider: Klin. Wchnschr. **6**:1037 (May) 1917.

17. Schneider, E.: Anaphylaxie und Roentgenstrahlen, Klin. Wchnschr. **6**: 1037 (May) 1927.

18. Coca, A. F.: Essentials of Immunology, Baltimore, Williams & Wilkins Company, 1926.

19. Mayr, J. K., and Moncorps, C.: Eosinophilia and the Spleen, München. med. Wchnschr. **73**:1777 (Oct.) 1926; Studien zur Eosinophilia, Virchows Arch. f. path. Anat. **264**:774, 1927.

TABLE 2.—*Allergic Asthma in Children* *

No.	Name	Age	Allergic History	Duration	Frequency of Attacks	Skin Sensitive to	Percentage of Eosinophilia	Additional Observations	Exposures		Number of Treatments	Observed For	Result	Comment
									First	Last				
1	Fle.	1	Eczema when 3 mo. old; urticaria	1	1 to 2 a week	Egg, rye, beans, tomatoes, oranges	11	.....	1/20/25	.....	1	5 mo.	+	Bronchopneumonia 1 month later
2	Mar.	5	Had eczema; four members of family had eczema	1	Every night	Egg	17	Chronic tonsillitis	7/26/25	8/ 4/25	2	3 mo.	+	Patient not seen after 3 months
3	Smi.	6	Negative	2	Every night	Almonds, barley, giant ragweed	7	Chronic choryza	10/ 6/25	9/21/26	2	16 mo.	++	
4	Mun.	3	Severe generalized eczema	1	1 to 2 a week	Egg, tomatoes	7	.....	11/10/25	5/11/26	2	13 mo.	++	Eczema not influenced; had varicellae after treatment
5	Egi.	5	Mother and uncle had asthma	3	1 in 2 weeks	Egg, milk	11	Adenoids	11/10/25	5/11/26	2	20 mo.	+	Free from attacks 1 year; then one attack
6	Dar.	11	Uncle had urticaria; grandmother had angioneurotic edema	7	1 a month	Oysters	3	Carious teeth	3/31/26	7/31/26	2	7 mo.	—	
7	Gro.	7	Aunt had eczema	3	Every 3 to 4 days	Milk	9	Tonsillitis	9/28/26	12/21/26	3	8 mo.	—	
8	Sch.	11	Frequent urticaria	8	Every 3 to 4 months	Eggs	9	.....	12/13/26	.....	1	10 mo.	+	
9	Tul.	7	Mother had hay-fever and asthma	5	2 to 3 a month	Several fish and meats	2	Carious teeth	5/31/27	.....	1	4 mo.	—	
10	Das.	12	Father had asthma and hay-fever; mother had urticaria	9	Every 2 to 3 weeks	Halibut herring	9	Carious teeth	6/14/27	7/25/27	3	4 mo.	—	
11	Jon.	3	Negative	1	Daily	B. coli	6	Chronic tonsillitis	7/24/25	8/25/25	4	6 mo.	++	
12	Spe.	10	Hay-fever; gastrointestinal disturbances	7	2 a week	Micrococcus catarrhalis, Streptococcus hemolyticus	5	Dental infection	9/ 8/25	.....	1	15 mo.	+	Well for 13 months; then few attacks
13	Ben.	9	Urticaria 4 years ago	4	1 in 2 weeks	Horse serum	14	.....	12/ 2/25	1/ 1/26	2	16 mo.	+	Well for 1 year; relapse after toxin-antitoxin injection
14	Rou.	6	Mother had hay-fever	2	1 a week	Streptococcus non-hemolyticus	14	Chronic tonsillitis	5/31/26	12/ 7/26	4	6 mo.	—	No improvement
15	Bro.	1½	Father had hay-fever; uncle had asthma	1	2 a month	Negative	6	Tonsillitis	11/23/26	1/25/27	2	10 mo.	++	
16	Hol.	4	Father had eczema; frequent urticaria	3	Every 1 to 3 nights	Streptococcus non-hemolyticus	3	Sinusitis	5/13/23	5/27/26	1	17 mo.	++	
17	Tos.	10	Eczema during infancy	1½	1 to 2 a week	Negative	8	Congenital syphilis	3/22/25	12/ 1/25	2	2½ yr.	+	Practically free from asthma now
18	Hal.	4	Father had asthma and hay-fever	3½	1 to 2 a week	Negative	6	Tonsillitis	3/ 8/27	3/29/27	3	4 mo.	—	

19	Guy.	6	Grandfather had asthma, formerly eczema	1	1 a week	Negative	..	Chronic tonsillitis	11/23/26	.....	1	12 mo.	++	
20	Hut.	6	Urticaria	4	Every night	Negative	3	Chronic tonsillitis	4/25/27	.....	1	6 mo.	+	
21	Kel.	4	Mother had hay-fever and asthma; sister had eczema	2	1 a month	Negative	..	Chronic tonsillitis	4/26/27	.....	1	6 mo.	++	
22	Sin.	8	Mother's father and father's mother had asthma; patient had eczema	5	Each fall for several weeks	Giant ragweed	3	.....	6/14/26	7/12/26	4	10 mo.	—	
23	McIs.	14	Hay-fever	7	Every 2 to 3 months	Giant ragweed	5	Chronic myocarditis	11/23/26	1/ 4/27	2	5 mo.	+	
24	Dec.	6½	Frequent vomiting after eating vegetables	4	1 in 1 to 2 weeks	Milk, casein, wheat, egg	4	Carious teeth	7/25/24	8/18/25	2	3 yr.	+	Had two slight attacks within 3 years
25	Zin.	12	Urticaria frequently	8	Every night	Cocoa, wheat, beans, chicken, pork	5	.....	9/ 8/25	9/25/25	2	13 mo.	++	Lethal nephrosis 1 year later after acute tonsillitis
26	Haz.	5	Mother and uncle had asthma	4	1 a month	Egg	8	.....	11/23/25	1/21/26	3	20 mo.	—	
27	Gab.	2½	Grandmother had asthma and hay-fever; child had urticaria	2	1 in 2 weeks	Egg, pneumococcus	11	Rhinitis	11/ 2/26	11/16/26	2	12 mo.	+	Had only one more attack
28	Kat.	3	Eczema when 6 months old	½	Every night	Milk staphylococci	6	Chronic tonsillitis	12/ 6/26	1/ 2/27	3	8 mo.	++	
29	Ker.	10	Sister had infantile eczema	5	Continuously for 4 months	Feathers	14	.....	9/ 7/26	9/21/26	3	13 mo.	++	Unusually severe case entirely free from attacks
30	Tar.	3	Vasomotor rhinitis (perennial)	1½	Every 3 weeks	Negative	2	Chronic tonsillitis	8/ 2/26	1/25/27	2	7 mo.	++	Had mastoid operation 5 months later
31	Pet.	12	Negative	10	3 a week	Negative	15	Chronic tonsillitis	9/21/26	9/28/26	2	4 mo.	—	
32	Urb.	9	Eczema	7	Every 3 weeks	Negative	5	Slight thyroid adenoma	6/26/27	.....	1	4 mo.	+	Well at present
33	Low.	4	Negative	3½	2 to 3 a week	Pollens and epidermis extracts	4	.....	11/ 9/26	1/11/27	2	5 mo.	+	
34	Fal.	10	Father had hay-fever; patient had urticaria	7	Every 2 weeks	Several bacteria and pollens	14	.....	3/15/27	4/23/27	3	3 mo.	—	
35	Cha.	5	Eczema	2	Every 2 to 3 nights	Egg, feathers	..	Chronic tonsillitis	11/25/24	12/ 9/24	2	3 yr.	+	
36	Wat.	6	Negative	1	Every night	Negative	9	Chronic tonsillitis	8/ 4/25	.....	1	6 mo.	—	
37	Cam.	3	Sister had eczema; grandfather had asthma	3	5 to 6 a year	Negative	..	.....	1/11/27	.....	1	10 mo.	++	
38	Max.	16 mo	Had urticaria; grandmother had asthma	1	1 every 2 to 3 months	Negative	5	.....	4/26/27	.....	1	6 mo.	+	
39	Cas.	6	Grandmother and mother had asthma	¾	1 to 2 a month	Negative	3	.....	5/10/27	.....	1	5 mo.	—	

* In the tables, + indicates that there was temporary relief; ++, symtom free and —, that the patient was not improved following treatment.

TABLE 3.—*Allergic Asthma in Adults*

No.	Name	Age	Allergic History	Asthma for Years	Frequency of Attacks	Skin Sensitive to	Percentage of Eosinophilia	Associate Observations	First Treatment	Last Treatment	Number of Exposures	Observed After Treatment For	Result	Comment
40	Bru.	50	Vasomotor rhinitis (perennial)	25	Daily	None	0	Emphysema	6/ 1/25	8/ 5/25	5	17 mo.	+	Relapse after 3 months
41	Ort	41	Sister had hay-fever and urticaria	10	2 to 3 a week	Horse dander; goose feathers; Streptococcus nonhemolyticus	5	.....	6/10/26	6/22/26	2	12 mo.	++	
42	Bah.	23	Hay-fever at age of 7 years	4	Every 2 to 3 nights	Streptococcus nonhemolyticus, Staphylococcus citreus	10	Septum deflection	8/17/26	8/24/26	2	14 mo.	+	Had two slight attacks only
43	Tho.	40	Hay-fever until 10 years ago; uncle had asthma	15	Every night	Staphylococcus aureus	14	One devitalized tooth	11/11/25	12/15/25	4	10 mo.	++	
44	Sta.	67	Sister had asthma	10	1 every second night	Negative	3	Septum deviation	3/ 9/26	4/10/26	2	3 mo.	+	Free from attacks for 3 months
45	Joh.	52	Brothers and sisters had eczema and urticaria	23	1 to 2 attacks a week	Herring	3	Tertiary syphilis	1/18/27	2/18/27	2	8 mo.	+	
46	Kno.	59	Eczema for 9 years; hay-fever	15	Continuously	Strawberry, egg, B. coli, Staphylococcus aureus	8	.....	7/13/25	8/25/25	3	19 mo.	—	Well since fall of 1926 without other therapy
47	Pla.	30	Brother had urticaria; mother had asthma	4	Every night	Staphylococcus aureus, nuts, celery	2	.....	5/23/27	6/ 1/27	2	6 mo.	—	
48	Win.	32	Mother and cousin had asthma; child had eczema	6	Daily	Almonds	4	Nasal polypi	4/12/27	6/ 7/27	4	5 mo.	—	Improved for 2 weeks, but subsequent relapse
49	Tho.	38	Two sisters of grandmother had asthma	1½	Days and nights	Acetylsalicylic acid	10	Ethmoiditis	6/ 6/25	8/ 7/25	3	1½ yr	+	Relieved 3 months; then as before
50	Mar.	33	Father and brother had asthma; baby had eczema	1	Daily	Meats and fish; tobacco	10	Thyroid adenoma	10/18/26	10/20/26	2	8 mo.	—	
51	Gan.	29	Mother and brother had asthma; sister had eczema	8	2 to 3 a week	Negative	3	Nasal polypus	3/15/26	4/12/26	2	19 mo.	++	

In the following studies in order to gain further insight into the influence of the spleen on allergic conditions, I have used roentgen-ray treatment over the spleen only. Irradiation of the chest was purposely omitted.

METHOD

In the cases recorded, the patients were under continuous observation during a period of from three months to three years. During this time, other treatment was not administered, with the exception of emergency measures during acute attacks. The patients were advised not to eliminate contact with known exciting substances. Patients with asthma who were sensitive to food were asked particularly not to exclude from their diet food to which they were sensitive.

The roentgen-ray treatment was administered by the roentgen-ray departments of the clinics. In the technic, the directions of Groedel were followed; 5 milliamperes, 4 mm. of aluminum, 88 kilowatts at 10 inch skin target distance were applied for six minutes. As a rule, two treatments were administered at intervals of two weeks. The number of treatments and intervals between treatments were, however, adjusted to the individual case (column 11 in tables 2, 3 and 4).

Before the treatment was instituted, the patients were carefully studied in an attempt to gain as much insight into the individual condition as possible. Skin tests, eosinophil counts and radiographs of the chest were made as routine procedures. In questionable cases, epinephrine was administered as a therapeutic test. Determinations of the blood calcium (Brown,[20] Wilmer[21]) were made for a number of patients, but later this was abandoned because the results were too inconstant to be of value in distinguishing allergic asthma from other asthma-like conditions. On the basis of these studies, the patients were grouped according to the etiology found (table 5).

In tables 2 and 3 are given the data for patients in whom the condition was definitely diagnosed as allergic asthma, in table 2 those of patients who were less than 15 years of age, and in table 3 those of patients 15 years of age or more. Following the procedure of Rackemann,[22] these patients were grouped according to their sensitiveness to bacteria, food, pollen and emanation. It should be noted, however, that this classification is not entirely satisfactory, because many asthmatic patients are sensitive simultaneously to several substances (Peshkin[23]). In table 4 are recorded the cases of hay-fever, angioneurotic edema, urticaria and eczema. Since these conditions are etiologically closely related to asthma, it was hoped to secure a broader view of the value of roentgen-ray therapy of the spleen by submitting these patients to this treatment. Table 4 also includes the data of cases in which the patients manifested

20. Brown, G. T.: Calcium Deficiency in Asthma, Hayfever and Allied Conditions, Ann. Clin. Med. **4**:299, 1925.

21. Wilmer, H. B.: Treatment of Bronchial Asthma, J. A. M. A. **89**:956 (Sept. 17) 1927.

22. Rackemann, R. M.: Clinical Classification of Asthma Based upon a Series of 648 Cases, Am. J. M. Sc. **162**:802 (Dec.) 1921.

23. Peshkin, M. M.: Asthma in Children, Am. J. Dis. Child. **31**:763 (June) 1926.

TABLE 4.—*Associated Conditions*

No.	Name	Age	Allergic History	Duration	Frequency of Attacks	Skin Sensitive to	Percentage of Eosinophilia	Additional Observations	First Exposure	Last Exposure	Number of Treatments	Observed After Treatment For	Result	Comment
						Allergic Bronchitis								
52	Ami.	6	Frequent vomiting after eating vegetables	1 yr.	1 to 2 a week	Cabbage, carrot, veal, chicken	9	Pyorrhea; carious teeth	11/12/24	2/24/25	4	3 yr.	++	Had chorea during observation
53	Kes.	9	Negative	6 mo.	Every morning	Negative	2	Negative	12/15/24	12/30/24	2	1 yr.	++	
54	Cau.	4	Eczema as baby; grandmother had asthma	2½ yr.	2 to 3 a week	Micrococcus catarrhalis, Streptococcus pyogenes, wheat	0	Infected teeth	9/21/26	9/28/26	2	5 mo.	+	
55	Sto.	13	Perennial rhinitis; eczema; mother had hay-fever	6 mo.	Daily wheezing	Oranges, tomatoes, prunes	12	Chronic tonsillitis	11/2/26	12/31/26	4	8 mo.	++	
56	Bre.	13	Eczema	1 yr.	Every night	Negative	3	Negative	4/10/27	.....	1	6 mo.	++	
						Tuberculosis and Asthma								
57	Eck.	9	Cousin had asthma	2½ yr.	Every second or third day	Negative	5	Formerly tuberculosis	2/17/25	11/24/25	3	2 yr.	—	Relief following tuberculin treatment
58	Nov.	6	Negative	1 yr.	3 attacks in 6 months	Pirquet	10	Beginning tuberculosis	8/11/25	11/24/25	3	9 mo.	—	Well for 10 months; died following pneumonia
59	Bor.	42	Urticaria; hay-fever	8 yr.	Constantly in winter	Negative	1	Tuberculosis	1/10/26	2/7/26	2	10 mo.	—	
60	Eri.	72	Negative	1 yr.	Every night	Negative	2	Tuberculosis	6/10/26	.....	1	9 mo.	—	
						Chronic Nonspecific Bronchitis Following Asthma								
61	Bal.	62	Had hay-fever	25 yr.	Every second or third day	Ragweed	10	Chronic myocarditis	11/27/25	.....	1	10 mo.	—	
62	Lev-	57	Had hay-fever	11 yr.	Every night	Negative	1	Maxillary sinusitis	9/24/26	12/6/26	2	1 yr.	—	
63	Har.	67	Had hay-fever and frequent urticaria	12 yr.	Every 3 or 4 days	Beans and fish	1	Chronic myocarditis	5/2/27	5/12/27	2	3 mo.	—	
						Bronchiectasis Following Asthma								
64	Sut.	37	Negative	35 yr.	2 to 3 a week	Tomatoes	2	Bronchiectasis	9/21/25	10/19/25	2	16 mo.	—	Relieved for 2 mo.

						Hay-Fever and Asthma								
65	Mer.	32	Hay-fever for 25 years; mother's family had asthma	20 yr	During hay-fever season only	Ragweed, timothy	9	None	8/ 7/26	.....	1	14 mo.	+	Had hay-fever, but no asthma
66	Ser.	30	One sister had asthma	9 yr.	1 to 2 attacks in season	Ragweed, timothy, orchard-grass	3	None	6/15/27	7/12/27	2	6 mo.	+	No hay-fever, no asthma
						Vasomotor Rhinitis (Perennial)								
67	Nas.	40	Hay-fever and angioneurotic edema	3 yr.	1 in 2 months	Chicken feathers, mustard, black pepper	1	Nasal polypus	5/27/27	.....	1	6 mo.	—	
68	Was.	5	Had urticaria; eczema	2½ yr.	3 in 2 months	Negative	1	Chronic bronchitis	4/21/25	.....	1	2 yr.	++	
69	Tut.	37	Choryza, hay-fever	4½ yr	Daily	Housedust and black pepper	3	Hemorrhoids; chronic tonsillitis	5/28/27	7/ 8/27	4	5 mo.	—	
						Urticaria								
70	Gif.	10	Negative	1 yr.	1 to 2 a week	Rabbit hair	6	None	5/26/25	.....	1	22 mo.	++	
71	Rub.	7	Mother had asthma	3 yr.	1 to 2 a month	Negative	6	Chronic tonsillitis	5/ 2/27	8/ 3/27	2	6 mo.	—	
72	Kay.	32	Negative	3 yr.	Every week	Negative	5	None	4/17/27	4/29/27	2	3 mo.	—	
						Angioneurotic Edema								
73	Rub.	40	Patient's child had asthma	3 mo.	4 times a week	Blue fish and herring	9	Chronic sinusitis; chronic salpingitis	6/17/27	7/14/27	3	4 mo.	+	
74	McGr.	19	Mother and grandfather had asthma	4 yr.	Every week	.....	7	Chronic tonsilitis	7/25/27	8/ 1/27	2	4 mo.	+	Only a few slight attacks lately
						Infantile Eczema								
75	Dia.	2	.....	1 yr.	.....	Negative	..	.....	12/ 8/25	12/10/25	2	5 mo.	—	
76	Macl.	14 mo.	.....	11 mo.	.....	Negative	..	.....	12/ 8/25	12/10/25	2	13 mo.	—	Very little improvement
77	Gro.	1	.....	3 wk.	.....	Negative	..	.....	12/22/25	.....	1	3 mo.	—	
78	Ram.	9 mo.	.....	9 mo.	.....	Negative	—	.....	3/31/27	.....	1	4 mo.	—	
						Thymus Hypertrophy								
79	Tar.	2½	Eczema when 4 months old	1½ yr	Every second or third day	Negative	8	Thymus hypertrophy	3/25/25	3/25/25	1	4 mo.	—	Well following thymus treatment
80	Sko.	4	Negative	3 yr.	1 in 2 to 3 nights	Egg, tomatoes	7	Chronic bronchitis, chronic tonsillitis	10/25/25	.....	1	3 mo.	—	
81	Bro.	1	Mother had asthma and hay-fever; uncle had asthma	5 mo.	Every night	.....	6	Rachitis	11/23/26	11/30/26	2	5 mo.	—	Treated successfully by thymus irradiation

the asthmatic symptom complex of wheezing and dyspnea, the cause of which was determined to be other than allergic, namely hypertrophy of the thymus. The cases of four patients with asthma on the basis of tuberculosis are also reported. The treatment was given to the two patients with hay-fever as prophylaxis before the expected onset of symptoms. Several patients with hay-fever received the roentgen-ray therapy during the season, but the results are not recorded because the treatment was administered too close to the expected time of the subsidence of symptoms to permit fair judgment of its value. In interpreting the results, I have relied on the patient's personal statement in conjunction with my own observation and the opinion of the referring

TABLE 5.—*Etiologic Classification of Cases*

Types	++	+	—	Total
Allergic Asthma (tables 2 and 3)				
Food	2	4	4	10
Pollen	—	1	1	2
Bacteria	7	8	2	17
Emanation	2	1	2	5
Food and pollen	1	1	—	2
Food and bacteria	1	1	3	5
Food and emanation	..	1	1	2
Pollen and emanation	..	1	..	1
Bacteria and pollen	..	..	1	1
Unknown causes	2	2	2	6
	15	20	16	51
Associated Conditions (table 4)				
Allergic bronchitis	4	1	—	5
Tuberculosis and asthma	—	—	4	4
Chronic nonspecific bronchitis following asthma	—	—	3	3
Bronchiectasis following asthma	—	—	1	1
Hay-fever and asthma (prophylactic treatment)	—	2	—	2
Vasomotor rhinitis	1	—	2	3
Urticaria	1	—	2	3
Angioneurotic edema	—	2	—	2
Infantile eczema	—	—	4	4
Thymus hypertrophy	—	—	3	3
	6	5	19	30

physician. The designation "symptom-free" (xx) is applied only to cases in which the patient has been under observation for at least six months following the treatment. The term "temporary relief" (x) indicates that the asthmatic attacks were markedly reduced in frequency as well as in severity for a limited lapse of time. This group includes some patients who were "symptom-free" when last seen, but who did not return for observation for a sufficiently long period of time to be classified in this group. The patients not relieved (—) were the ones who did not show improvement within three weeks after the last exposure. Other therapeutic measures were administered to these patients later, and a considerable number were improved, but their relief from symptoms was not attributed to the roentgen-ray therapy. As a whole, an attempt was made to be conservative in interpreting the results. The designation "cured" has purposely not been used, because one should be

aware of the fact that even though a patient is symptom-free for several years, an attack is apt to occur at some future time.

RESULTS

In a total of eight-one cases, twenty-one patients were symptom-free, twenty-five were temporarily relieved and thirty-five, of 43.2 per cent, did not respond to the treatment. Of fifty-one patients with allergic asthma (tables 2 and 3), fifteen remained symptom-free, twenty were temporarily relieved, and sixteen did not respond to the treatment, representing 31.3 per cent of failures.

In table 2 the records of thirty-nine children show 30.8 per cent of failures; in table 3, presenting twelve adults, the figures show 33.3 per cent of failures. Table 4 shows the results of treatment of patients suffering from asthma complicated by other conditions and also patients with other allergic diseases; only six of thirty patients

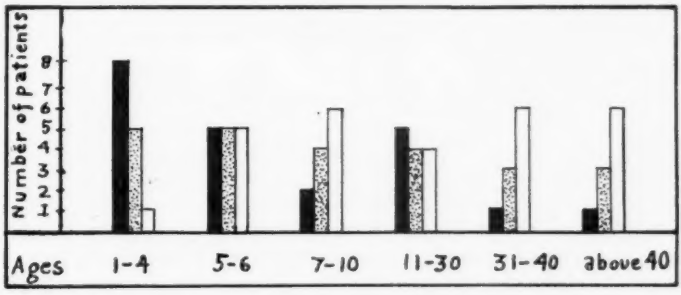

Fig. 1.—Efficacy of treatment in patients of various ages. The black columns indicate that the patients were symptom free; the dotted columns that there was temporary relief and the blank columns that the patients were not improved.

were symptom-free; five were temporarily relieved, and nineteen, or 63.3 per cent, did not respond. The details are given in table 5, which reveals that patients who had asthma complicated by tuberculosis or chronic bronchitis (emphysema) did not show improvement. Likewise, patients with eczema and "asthma" due to hypertrophy of the thymus did not benefit by the treatment. The results in cases of hay-fever, urticaria and vasomotor rhinitis are uncertain. In patients with allergic bronchitis, the treatment was most effective. Allergic bronchitis is a condition characterized by cough and expectoration due to allergy, but it is not sufficiently severe to produce attacks (Duke[24]). The results in table 5 also indicate that in bacterial cases the patients were relieved

24. Duke, W. W.: Allergy, Asthma, Hay-Fever and Allied Manifestations, St. Louis, C. V. Mosby Company, 1926.

by this treatment more generally than in other cases. The age of the patient furnished information that was of some prognostic value. An analysis of figure 1, in which the age of the patients is compared with the efficacy of the treatment, indicates that the greatest number of improvements occurred in the younger and the greatest number of failures in the older patients.

REACTION

Most observers noticed a marked "reaction" after the treatment, consisting mainly of nausea, vomiting, headache, dizziness and, occasionally, a severe attack of asthma. Groedel expressed the opinion that this reaction may possibly be an obligatory factor to a subsequent cure, and he felt that the severity of the reaction was in direct proportion to the degree of relief obtained. Gerber believed that the occurrence of the reaction is due to the administration of too large doses of the roentgen ray. On restricting the exposures to the mediastinum only, he observed less severe reactions. Observations in regard to this question are recorded in table 6. One hundred and sixty-nine treatments were administered to eight-one patients. Of this number, only thirty-seven treatments given to thirty-three patients were followed by reactions.

TABLE 6.—*Observation on Reactions*

Case	Exposure on	Reaction*	Days Following Treatment	Result
2	7/26/25	V. N.	5	+
	8/ 4/25	D.	2	
3	9/21/26	P.	2	++
4	10/13/25	V.	1	++
5	11/10/25	V. N.	2	+
	5/11/26	P. V.	2	
6	3/31/26	V.	1	—
7	12/21/26	V. P.	4	—
8	12/13/26	P.	2	—
12	9/ 8/25	V. P. A.	2	+
13	12/ 2/25	D. V. P. A.	2	+
14	5/21/26	D.	1	—
17	3/22/25	N. A.	4	+
21	4/26/27	N.	1	++
24	11/23/26	D. V.	5	+
25	9/ 8/25	N. D.	2	++
26	11/23/25	V. N.	1	—
28	1/ 5/27	V. A.	2	++
32	6/26/27	A.	1	+
34	4/23/27	N. D.	2	—
42	8/24/26	N. V. P.	2-5	+
48	4/12/27	V. N. D.	1	+
49	7/21/25	P. N.	3	+
51	3/15/26	V. N.	1	++
52	11/12/24	A.	5	++
53	12/15/24	V.	2	++
55	11/ 2/26	V. N.	2	++
	11/19/26	D. P.	2	
59	11/23/27	V.	1	—
60	11/30/25	N. V. P.	3	—
62	1/10/25	V.	2	—
63	6/10/26	N.	2	+
65	9/24/26	P. N. V.	1	++
68	8/ 7/26	N.	2	+
72	5/28/27	N. V.	2	—
	7/ 8/27	N.	2	
79	12/ 8/25	V.	2	+

* N. indicates nausea; V., vomiting; P., abdominal pain, and A., asthmatic attack.

Ten of these patients were symptom-free, thirteen were temporarily relieved and ten did not improve. There were, therefore, only 30 per cent of failures among these cases as compared with 43.2 per cent of the whole total. Thus, on the whole, the occurrence of a reaction was accompanied by better results. The severity of the reaction in the individual case, however, did not determine the degree of relief, as a close analysis of table 6 reveals. The reaction usually occurred on the second day; nausea and vomiting were the predominating symptoms. In five cases, a severe attack of asthma followed the treatment; in one, a marked urticaria. In one patient who was treated after the conclusion of these studies, extensive eczema developed on the site of exposure, whereas the asthma disappeared completely.

LUNGS

Groedel, Gerber, Mueller and others noticed a marked increase in expectoration among the patients who improved. I did not always observe this phenomenon. Some patients developed a severe, dry,

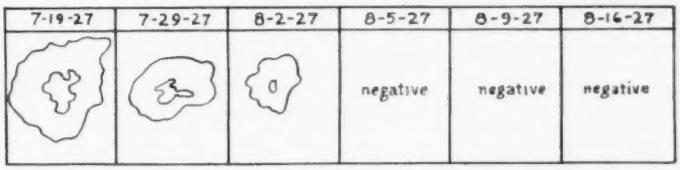

Fig. 2 (case Skok).—Variation of skin reaction (egg) following irradiation of the spleen. Treatment was given on July 26, 1927.

unproductive cough which lasted from one to two weeks, apparently taking the place of the asthmatic attacks. In patients 29 and 51, in whom this peculiar bronchitis was seen, the subsequent relief from asthma was extremely spectacular. On reexamination of the chest by the roentgen ray after the treatment, however, definite changes in the appearance of the glands of the hilum were not detected. The patients designated as "symptom free" were entirely free from the physical signs of asthma on frequent reexamination of the lungs. In a few cases, hyperresonance of the percussion note was the only sign encountered.

SKIN TESTS

In all previous reports on roentgen-ray treatment for asthma, reference to skin tests has not been made. In this study, as a rule, parallelism was not observed between the diminution in the size of the area sensitized and the improvement of the patient. In some instances, however, the positive reaction of the patient became negative as he improved. This change occurred within the first five or six days following the

treatment (fig. 2 and table 7). A change in the size of the sensitized area was not found within the first twenty-four hours. In some patients, the reaction to the skin tests remained negative for months. On

TABLE 7.—*Record of Percutaneous Skin Tests in Case 1 Before and After Treatment Which Was Given on Jan. 20, 1925*

January 16		January 21—One Day After Treatment		January 26—Six Days After Treatment	
Beef	—	Beef	—	Beef	—
Chicken	—	Chicken	—	Chicken	—
Milk	—	Milk	—	Milk	—
Eggs	+++	Egg	++	Egg	—
Rye	+	Rye	—	Rye	—
Oats	—	Oats	—	Oats	—
Corn	—	Corn	—	Corn	—
Beans	+	Beans	—	Beans	—
Spinach	—	Spinach	—	Spinach	—
Tomatoes	+	Tomatoes	—	Tomatoes	—
Strawberries	—	Strawberries	—	Strawberries	—

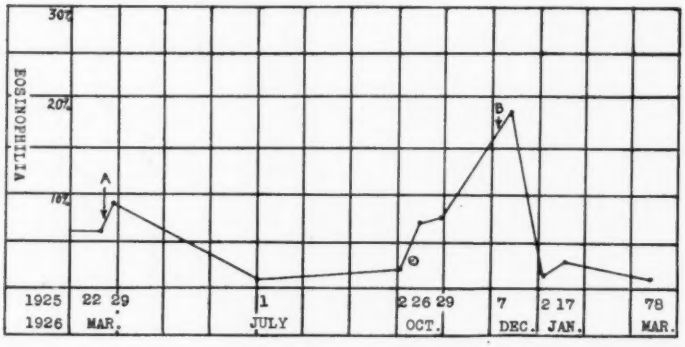

Fig. 3 (case 17).—Effect of irradiation of the spleen on eosinophilia. *A* indicates the first and *B* the second roentgen-ray treatment. The patient had one or two attacks per week preceding treatment. The dotted circle indicates the occurrence of the only attack during the period of treatment.

the other hand, a patient (23) in whom a 3 plus ragweed test never became negative was freed from asthma and hay-fever.

EOSINOPHILIA

Previous observers (Pohlman, Mueller and others) report a decrease in the number of eosinophil cells following the treatment. In the majority of cases I had the same experience, with the exception, however, that within the first one or two days, hypereosinophilia was noted (fig. 3). When the blood was examined within the first two or three hours, I found an increase in eosinophilia already present. The eosinophilia reached its highest degree at the time of reaction, and it

usually decreased below its original level within the first two or three weeks following. In patients in whom a high eosinophilia was present, a further increase did not take place. This is exemplified by case 29 (fig. 4). A relationship did not exist between the degree of eosinophilia before the treatment and the degree of improvement obtained (table 8).

TABLE 8.—*Relationship of Efficacy of the Roentgen-Ray Treatment Over the Spleen to Eosinophil Count Previous to Treatment*

Number of Cases with Eosinophilia of	Result			Total	Percentage of Failures
	++	+	—		
0 to 5 per cent	8	14	14	36	39.7
6 to 10 per cent	7	6	13	26	50
11 to 15 per cent	3	5	2	10	20
Above 15 per cent	—	1	—	1	—
	18	26	29	73	

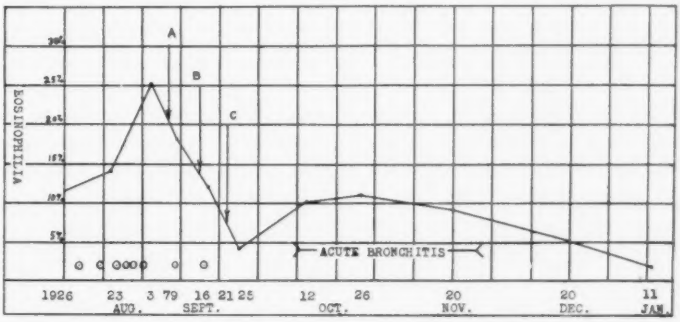

Fig. 4 (case 29).—Effect of irradiation of the spleen on eosinophilia. *A*. indicates the first exposure; *B*, the second, and *C* the third. The dotted circles indicate the occurrence of attacks of asthma. The patient did not have any attacks following the third exposure.

COMMENT

The explanation of these results is difficult, since the knowledge both of the relationship of the spleen to allergy and of the etiology of asthma itself is too vague to make any definite conclusion possible. Many theories are offered by the various authors. Groedel speculates on the possibility of stimulating the function of the spleen by the roentgen ray. He thinks that certain substances might thus be activated to counteract the allergic state. On the basis of this theory, Gasul employs diathermic treatment of the spleen as a means of stimulating this organ. Gerber assumes that destruction of tissue of the spleen rather than its stimulation might be the effect of roentgen-ray therapy. He holds that the

foreign protein created by the destroyed tissue of the spleen is responsible for the relief obtained. Such a theory is plausible in view of the great improvement achieved in the treatment of patients with asthma by the parenteral use of various foreign protein agents, such as tuberculin (van Leeuven and Varekamp [25]), vaccine (Brown [26]), peptone injections (Pasteur Vallery-Radot [27]) and many others.

In a previous publication,[11] I showed that the reticulo-endothelial system as well as the lymphatic apparatus might be involved in the process of production of antibodies. In both of these systems, the spleen plays an important rôle. In spite of the extensive research to determine the function of the spleen, the question of the relationship of these two systems to allergy has not as yet been sufficiently considered. The outcome of the foregoing studies warrants further investigation in this matter.

The question arises as to how much of the improvement observed in these patients is due to psychic influence (Nietzsche, Levy-Dorn [28]). Since the classical work of Walker,[29] the old theory of "asthma nervosum" has been abandoned. Recent contributions to literature (Ziegler and Elliott [30]), however, make it probable that the mental status of a person has at least some bearing on the elicitation and termination of asthmatic attacks. I attempted to give my patients as little encouragement concerning the efficacy of the treatment as possible. Most of the children were submitted to the treatment with the idea that it was "just another test," and they returned relieved without realizing that a treatment had been administered. Several children were less than 2 years of age; among these the possibility of a psychic "cure" can be definitely ruled out.

In applying a measure such as roentgen-ray treatment over the abdomen, one should be aware of the fact that there are several objections, at least theoretically, to such a treatment for a benign disease. One might speculate on the possibility of exciting a latent cancerous growth in the irradiated area. Moreover, a destruction of the tissue of the spleen might cause a permanent change in the blood picture or might

25. Van Leeuven, W. S., and Varekamp, H.: Tuberculin Treatment of Bronchial Asthma and Hay-Fever, Lancet **12**:1366 (Dec.) 1921.

26. Brown, G. T., and Hunter, A.: Bacterial Vaccines in Asthma, Am. J. M. Sc. **171**:156 (Jan.) 1926.

27. Pasteur Vallery-Radot and Blamontier: Intradermal Injections of Peptone in Treatment of Anaphylactic Diseases, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:491 (May) 1927.

28. Nietzsche, Levi-Dorn, quoted by Groedel (footnote 4).

29. Walker, I. C.: Studies on Sensitization on Patients with Bronchial Asthma, J. M. Research **35**:487, 497, 509, 1917.

30. Ziegler, L. H., and Elliott, D. C.: The Effect of Emotion on Certain Cases of Asthma, Am. J. M. Sc. **172**:860 (Dec.) 1926.

lower the resistance of the patient against intercurrent infections. Careful search has been made for any such occurrence. Although irradiation of the spleen has been widely employed on the continent since 1921, when Stephan [31] advocated its application for controlling hemorrhage, adverse sequelae have not been reported in the literature. Harbinson [32] failed to find any pathologic changes in the blood picture in postmortem and clinical studies on rabbits that had received doses of roentgen ray many times larger than those administered to human beings. Furthermore, it has been said that the spleen may be removed from the human body without ill effect.

Frequent examinations of the blood were made in some of the patients for three years following the treatment, and indications of pathologic changes in the blood were not discovered. There were, however, two occurrences which should not be omitted from this report. In case 25, the patient remained entirely free from asthma for one year but nephrosis developed thirteen months after the treatment which resulted in death. In case 59, the asthmatic condition was improved for ten months, but the patient succumbed to fulminating pneumonia which appeared to be tuberculous in origin. The death of these children cannot be attributed to the treatment; the allergic disease itself might have impaired the resistance of these patients to infection, or, what is more probable, the intercurrent events did not bear any relationship to the original condition. On account of this experience, however, one should use discretion in applying this treatment.

SUMMARY

1. Eighty-one patients with asthma and associated allergic conditions were treated with small doses of roentgen ray over the spleen. Eighteen of fifty-six children became symptom-free; sixteen were temporarily relieved, and twenty-two did not respond to the treatment. Three of twenty-five adults became symptom-free; nine were temporarily relieved, and thirteen were not improved. In other words, there were 39.4 per cent failures among the children and 52 per cent among the adults. The patients designated as "symptom-free" were under observation for a period of time varying between six months and more than three years.

2. Patients less than 4 years of age showed the best results, and the treatment in patients more than 30 years of age was less effective. Patients afflicted simultaneously with tuberculosis and the chronic emphysematous type of asthma did not respond to the treatment. In cases of infantile eczema and an hypertrophying thymus, the condition

31. Stephan, R.: Blutung und Blutstillung, München. med. Wchnschr. **68**:746 (June) 1921.

32. Harbinson, C. H.: The Effect of Roentgen-Ray Energy on the Spleen, J. M. Research **67**:529, 1924.

did not improve. The best results were seen among the patients with a beginning allergic condition manifested by allergic bronchitis. Better results were obtained among patients with asthma who were sensitive to bacteria than among those sensitive to food, pollen and emanation.

3. In some patients who improved, the positive skin tests became negative within the first week after the treatment.

4. As a rule, the number of eosinophils increased immediately after the treatment and returned to normal subsequently. A relationship did not exist between the degree of eosinophilia preceding the treatment and the efficacy of the irradiation of the spleen.

5. Thirty-seven of a total of 169 exposures were followed by reactions characterized by vomiting, nausea, abdominal pain or an asthmatic attack from one to five days after the treatment. Better results were encountered among these patients.

6. The value of the treatment is discussed, and warning is given against its indiscriminate use. The opinion is expressed that it should be applied only in cases of allergy in which the patients do not respond to the ordinary methods.

After the completion of the foregoing studies, the patients in the following additional cases reported at the clinic following the roentgen-ray treatment.

REPORT OF ADDITIONAL CASES

CASE 82.—Skok, a boy, aged 4, gave a history of having had attacks of asthma for the past two years, which were promptly brought on by ingestion of eggs. They were usually associated with vomiting and dry cough and responded to treatment with epinephrine. Two brothers had eczema; otherwise the family history was negative regarding allergy. The patient had previously attended the clinic for patients with heart diseases, where a diagnosis of congenital pulmonary stenosis was made. Aside from these observations, the physical examination revealed poor expansion of the lungs, a few asthmatic bruits and silent hyperresonance. Skin tests with a large number of extracts were negative, with the exception of a 3 plus reaction to the skin test for eggs.

The patient was given one roentgen-ray treatment over the spleen on July 26, 1927. Several hours subsequent to the treatment, he had had a slight attack of vomiting. The appearance of the skin reaction is given in figure 4. He developed a dry, convulsive cough on August 2, which lasted until Aug. 26, 1927. With the exception of a slight attack of wheezing on November 25, which his mother attributed to an infection of the upper respiratory tract, he has been free from attacks and has been able to eat eggs without discomfort.

He was last seen on Feb. 3, 1928, when the skin test for egg was negative.

CASE 83.—Beb, a boy, aged 3, presented a history of having had severe asthmatic attacks for the past two years. They were often preceded by colds and were inevitably elicited by eating apples. The mother's cousin and great grandmother had had asthma. True asthmatic attacks were demonstrated on several occasions when the child ate apples in the clinic. The physical examination made during an attack revealed the typical signs of asthma; the attacks were relieved by treatment with epinephrine. A series of intradermal skin tests

revealed: reaction with apples, 2 plus, and *Staphylococcus aureus,* 1 plus. There was an eosinophilia of 5 per cent.

The roentgenogram of the chest revealed some hypertrophy of the hilum glands. There was no evidence of tuberculosis, thymus hypertrophy and bronchiectasis.

The child was given two roentgen-ray treatments on Nov. 1, 1926, and on December 7. On December 9, the blood count showed 16 per cent eosinophils. At this time, the child was slightly dyspneic. He has never had another attack since. On May 3, 1927, the eosinophil count was 1 per cent, the skin tests were negative and the child could eat apples without distress. Owing to the fact that he suffered from a cough which appeared to be an allergic bronchitis, however, the patient was given another treatment on May 24, 1927. This treatment did not elicit a reaction.

On Feb. 24, 1928, the mother said that the boy had never had another attack of asthma. He rarely has colds now. The results of physical examination were negative.

CASE 84.—La Fr, a boy, aged 3½ years, had had bronchial asthma for two years. The attacks occurred every third or fourth week. Several members of the mother's family had suffered from asthma, hay-fever and eczema. During the first year of his life, he had frequent convulsions, which the mother attributed to the ingestion of eggs. She also said that the odor of mustard nauseated him and that once, after a mustard plaster was put on his chest, he had a severe seizure of urticaria. When first examined on Sept. 23, 1927, there was a papulous exanthem distributed over the buttocks. The skin tests revealed sensitiveness to eggs, cheese, peas, mustard, black pepper, timothy and Bermuda grass. An eosinophilia of 5 per cent was present. The nose and throat clinic reported congestion of the turbinate on both sides. The examination of the chest, which was made during an interval between attacks, showed slight hyperresonance. The asucultation was normal. The patient received one roentgen-ray treatment over the spleen on October 11. The following day, marked eczema developed over the irradiated area, which had thus far been normal in appearance. The condition on the skin disappeared after two days. On March 3, 1928, the mother reported that the child had been feeling much better, and that he had had only one slight attack, which occurred in November. He could eat eggs and was no longer affected by the odor of mustard. The skin had been clear since the treatment.

CASE 85.—New, a girl, aged 7, had had attacks of asthma for three years. They were usually brought on by damp weather, and always occurred when the child approached the furnace in the basement. The family history was negative regarding allergy.

The examination, which was made during the interval between attacks, revealed marked pharyngitis, several enlarged submaxillary glands and chronic maxillary sinusitis. This diagnosis was confirmed by a consultation with a specialist on diseases of the nose and throat. The chest was normal, but the roentgenogram showed a marked bilateral tracheobronchial adenopathy. There was no evidence of enlargement of the thymus. The skin tests were negative; however, a former examination at another institution had revealed sensitiveness to dog hair, cat hair and goose feathers. There was an eosinophilia of 2 per cent. The patient was given roentgen-ray treatment over the spleen on Nov. 22, 1927. The following day the child developed a slight attack of asthma. On March 12, 1928, she was reexamined. She has not had any attacks since the treatment.

1054-1056 Maccabee Building.

COARCTATION OF THE AORTA*

L. MINOR BLACKFORD, M.D.
Fellow in Medicine, The Mayo Foundation
ROCHESTER, MINN.

Coarctation of the aorta signifies a constriction of the aorta in the region of its juncture with the ductus arteriosus or its vestige. The term, congenital stenosis of the isthmus, is also employed. The advantage of this term is that it is, as King [1] has remarked, more easily understood by persons who do not read English readily. The disadvantages outweigh this, for the term is clumsy and subject to ambiguous abbreviation. Many authors have maintained that the condition develops after birth. The anatomic isthmus is that part of the aorta between the origin of the left subclavian and the mouth of the ductus arteriosus; this definition excludes the large number of cases reported in which the constriction is distal to the insertion of the ligamentum arteriosum. However, in 1839, Mercier [2] wrote "coarctation" in French; ten years later Diesterweg,[3] "coarctatio" in Latin, and the English word coarctation has an honorable history of fifty-two years.

According to Barié [4] and others, the first case definitely described was recorded by Paris in 1791. An idea as to the incidence of coarctation may be gained from the statistics of a large number of necropsies. If conclusions may be drawn from the figures in table 1, coarctation occurs once in about 1,550 cases. Of about 200 cases in adults already reported, only nineteen were definitely recognized during life, although obstruction of the thoracic aorta was diagnosed in six additional instances. These facts can mean only that the anomaly is frequently overlooked or unrecognized.

---

* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine, December, 1927.

1. King, J. T., Jr.: Stenosis of the Isthmus (Coarctation) of the Aorta and Its Diagnosis During Life, Arch. Int. Med. **38**:69 (July) 1926.

2. Mercier, A.: Rétrécissement avec oblitération presque complète de la portion thoracique de l'aorta, Bull. et mém. Soc. anat. de Paris **14**:158, 1839.

3. Diesterweg, C. A.: De aortae obliteratione, singulari modo involutionis ductus arteriosi Botalli perfecta, Berolini, G. Schrade, 1849, p. 40.

4. Barié, E.: Du rétrécissement congénital de l'aorte descendante, Rev. méd. **6**:342-366, 409-442, 501-516, 1886.

DEVELOPMENT

A discussion of this subject can be made more intelligible through an epitome of the early development of the vascular system.[11] At the 3 mm. stage, two aortas leave the aortic sac and are continued caudad through the first pair of branchial arches as the dorsal aortas, which communicate with the placenta. The first arches are moored by the first pharyngeal pouches, and the disproportionate growth of the adjacent structures demands a more direct communication between the heart and the dorsal aortas; thus the fusion of sprouts from the aortic sac and from the paired aortas form the successive branchial arches, as the first two pair disappear. Meanwhile through expansion and growth, fusion of the dorsal aortas progressing cephalad has begun. The pulmonary arch on each side arises from the caudal wall of the aortic sac, and it may open into the aorta at a distinct interval from the fourth arch, close to it, or with it (fig. 1).

TABLE 1.—*Coarctation Revealed at Necropsy as Reported in the Literature*

Lochte [5]	4 in 10,000	(approximately)
Fawcett [6]	18 in 22,316	
Jaffe and Sternberg [7]	1 in 4,500	
Meixner [8]	16 in 21,481	
Hansteen [9]	4 in 10,000	(approximately)
Ophüls [10]	1 in 3,000	
Total	44 in 68,300	(approximately)

At this period the seventh cervical segmental arteries, which will largely form the subclavians, spring from the dorsal aspect of the unpaired aorta. Apparently because its largest branch, the vertebral, is fixed by the cervical vertebrae, each subclavian moves cephalad on to its respective dorsal aorta and ascends it when the aortas are pulled caudad

5. Lochte, quoted by Reinitz: Ueber congenitale Stenose und Obliteration am Isthmus aortae, Kiel, Schmidt und Klaunig, 1908.

6. Fawcett, J.: Coarctation of the Aorta as Illustrated by Cases from the Postmortem Records of Guy's Hospital from 1826-1902, Guy's Hosp. Rep. **59**:1, 1905.

7. Jaffe, R. H., and Sternberg, Herman: Kriegspathologische Erfahrungen, Virchows Arch. f. path. Anat. **231**:346, 1921.

8. Meixner, Karl: Berstung der aufsteigenden Körperschlagader bei Verschluss am Ende des Bogens, Beitr. z. gerichtl. Med. **5**:72, 1922.

9. Hansteen, E. H.: Medfødt aorta-stenose, Norsk. Mag. f. Laegevidensk. **86**:1073 (Oct.) 1925.

10. Ophüls, W.: A Statistical Survey of Three Thousand Autopsies from the Department of Pathology of the Stanford University Medical School, Univ. Ser. Med. Sc., Palo Alto **1**:131, 1926.

11. Congdon, E. D.: Transformation of the Aortic-Arch System During the Development of the Human Embryo, Contrib. Embryol., Carneg. Inst., Washington **14**:47, 1922.

with the descent of the heart into the thorax; it is not until the end of the seventh week (18 mm. stage) that the left subclavian reaches its definitive position close to the origin of the left common carotid. By the 14 mm. stage, however, the aortic sac has been divided into the definitive aorta and pulmonary trunk, and the breaking up of the branchial arch system is now effected rapidly, principally by atrophy of four parts of the vascular system, the segment of each dorsal aorta between the third and fourth arches, the caudal end of the right paired aorta, and the distal part of the right pulmonary arch. Congdon attributes these interrup-

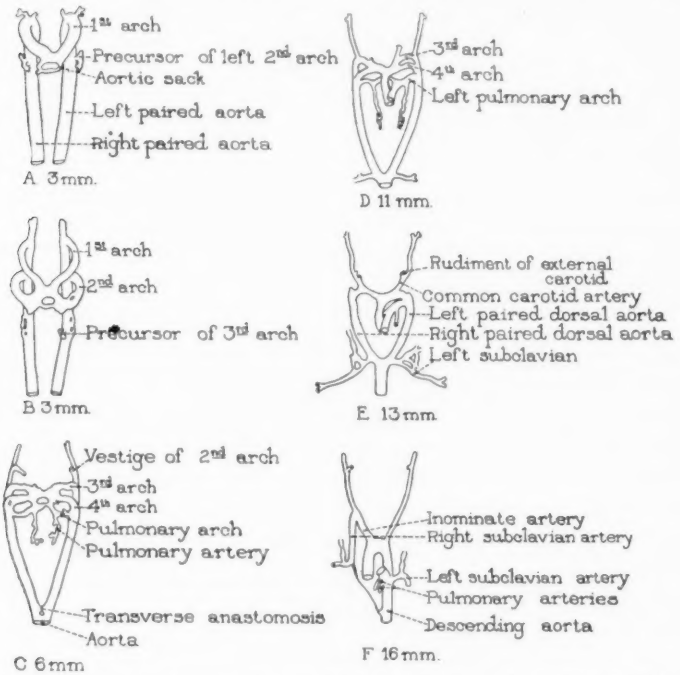

Fig. 1.—The development of the aortic-arch, drawn from reconstructions. (After Congdon.)

tions to reduction of the blood-flow through the affected segments. In specimens studied by him, he described the changes as follows:

The fourth arch region, which was at the summit of the forming definitive arch, sinks to the descending limb, and the region of the left common carotid, now shared by the innominate, comes to constitute the entire summit. The region of the arch derived from the fourth arch increases rapidly in diameter to reach in cross-section an approximate equality with the more proximal and distal parts derived from vessels which are already capacious at the beginning of the branchial period.

The fourth arch is, however, usually considered to have been the primordium of the isthmus.

The interventricular septum is completed by the end of the second month and no further radical change takes place in the cardiovascular system until the obliteration of the ductus arteriosus after birth. In 1826, Kilian [12] first announced that this was effected through the change in blood pressure due to the expansion of the lungs. In 1852, Rokitansky [13] stated that the ductus was obliterated through an uneven proliferation of the intima. Schaeffer and Radasch [14] recently corroborated this, and attribute it to the atrophy of disuse, as is found in other parts of the body. Walkhoff [15] and Langer [16] showed that fibers from the ductus do not normally extend into the walls of the aorta; Bartels [17] interpreted this to mean that they never do.

PATHOGENESIS

Reynaud [18] (1828) considered coarctation a persistence of the fetal state in some way influenced by the involution of the ductus. Rokitansky [13] (1852) was in essential agreement. In 1887, Loriga [19] maintained that the ductus arteriosus did not play a part in the pathogenesis, and that the anomaly could be traced back to intrauterine life, the differing pathologic types corresponding to the differing periods at which the lesion began. Dickinson and Fenton,[20] Minkowski,[21] Mönckeberg [22] and Meixner [8] believe it is of developmental origin. Meixner considers the atherosclerotic changes so often found in the aorta usually proximal but sometimes just distal to the stenosis owing to the

12. Kilian, quoted by Klotz: Tr. A. Am. Phys. **22**:213, 1907.

13. Rokitansky, quoted by Barié (footnote 4); by Bonnet: Rev. de méd. 1903, vol. 23; by Klotz (footnote 12); by Sankott: Anat. Anz. **48**:261, 273, 1915.

14. Schaeffer, J. P., and Radasch, H. E.: On the Obliteration of the Lumen of Blood Vessels; the Origin and Nature of the Mass which Comes to Occupy the Lumen of an Artery Segment Between Two Ligatures, Am. J. Anat. **33**:219, 1924.

15. Walkhoff, quoted by Knierim: Ein Fall von Stenose der Aorta in der Gegend der Insertion des ligamentum arteriosum, Marburg, 1880, p. 1; by Bartels: Hospitalstid. **5**:1549, 1912.

16. Langer, quoted by Knierim and by Bartels (footnote 15).

17. Bartels, C. D.: Et tilfaelde af stenosis aortae congenita, Hospitalstid. **5**: 1549, 1912.

18. Reynaud, quoted by Knierim (footnote 15, first reference); Barié (footnote 4); Bonnet (footnote 13, second reference) and others.

19. Loriga, G.: Stenosi ed obliterazione congenita dell' aorta, Riv. clin. di Bologna **7**:529, 1887.

20. Dickinson, W. L., and Fenton, W. J.: A Case of Complete Coarctation of the Arch of the Aorta; Necropsy, Lancet **2**:1196, 1900.

21. Minkowski, Oscar: Ein Fall von Stenose der Aorta an der Einmündungsstelle des Ductus Botalli (isthmus aortae persistens), München. med. Wchnschr. **48**:1335, 1901.

22. Mönckeberg, quoted by Lützow-Holm: Norsk. Mag. f. Laegevidensk. **86**:1066 (Oct.) 1925.

overdistention of the vessel, which experiences a tug at each fixed point, such as the origin of the intercostals, but especially at the insertion of the ligamentum arteriosum.

The prenatal development of coarctation in all cases has never been universally accepted. Kaufmann,[23] Zenoni [24] and others attribute it in some cases at least to the propagation of an inflammatory process in the ductus botalli to the walls of the aorta. In 1844, Hamernjk [25] observed that the constriction might be proximal to, at the site of, or distal to, the aortic opening of the ductus arteriosus, and accordingly divided these cases into three types; he accepted Reynaud's theory for the first, but seems to have supposed that prolongation of the thrombus hypothesized in the closure of the ductus was responsible for the other two forms. In 1855, Skoda [26] argued that fibers from the ductus extended into the aortic wall, and that these fibers contracted with the contraction of the ductus in the process of its obliteration. In 1900, Schlesinger [27] revived the theories of both Reynaud and Skoda. Three years later, Bonnet [28] elaborated these two hypotheses. In fact, according to Bonnet, constriction of the aorta proximal to the mouth of the ductus arteriosus dates from intra-uterine life and, if not a transient persistence of the normal fetal state, is incompatible with life for more than a brief period. On the other hand, constriction at or distal to the ductus he explains by Skoda's theory, and finds it devoid of influence on the health or longevity of the person except that it may predispose to endocarditis. He called these, respectively, the infantile ("type du nouveau-né") and the adult types. Abbott [29] offered this explanation in 1927.

It has been intimated several times [30] that syphilis may cause coarctation, but striking arguments have not been adduced in support of the theory.

---

23. Kaufmann, Eduard: Lehrbuch der speziellen pathologischen Anatomie, ed. 8, Berlin, Georg Reimer, 1922, vol. 1, pp. 69-70.

24. Zenoni, C.: Occlusione completa dell' aorta discendenta, Arch. per le sc. med. **35**:1, 1911.

25. Hamernjk, quoted by Diesterweg (footnote 3); by Knierim (footnote 15, first reference) and others.

26. Skoda, quoted by Knierim (footnote 15, first reference); by Barié (footnote 4); by Bonnet: Rev. de méd., 1913, vol. 23, and by others.

27. Schlesinger, Hermann: Stenosis of the Aorta Near the Duct of Botalli, Internat. Clin. **4**:140, 1900.

28. Bonnet, L. M.: Sur la lésion dite sténose congénitale de l'aorte dans la region de l'isthme, Rev. de méd. **23**:108-126, 255-265, 335-353, 418-438, 481-502, 1903.

29. Abbott, M. E.: Coarctation of the Aorta: Hypoplasia of the Aorta and Its Branches, Anomalies of the Aortic Arch, in Osler and McCrae, Modern Medicine, ed. 3., Philadelphia, Lea & Febiger, 1927, vol. 4, pp. 772-794.

30. Edelmann, A., and Maron, R.: Die Isthmusstenose der Aorta und ihre Differentialediagnose, Wien. Arch. f. inn. Med. **4**:1 (April) 1922. Koster and Forselius: Fall af total stenos i aorta, Hygeia **77**:935, 1915.

PATHOLOGY

Bonnet's division into the infantile and adult types simplifies discussion of the pathology of coarctation. As found in fetuses, stillborn and young infants, coarctation is usually a diffuse narrowing of the isthmus of the aorta, but this segment may be represented by a fibrous cord or be altogether lacking. The ductus is patent in almost inverse ratio to the lumen of the isthmus, and where the latter is atresic, the pulmonary trunk is continued with undiminished diameter into the descending aorta. With one exception,[8] there is no collateral circulation. Grave developmental defects of the cardiovascular system in other parts of the body are common.

The aorta in the case of adults (and occasionally of infants dying from other causes) appears as though it had been more or less tightly ligated at or just distal to the ductus arteriosus, which is usually distal to the origin of the left subclavian but is in a few cases proximal. The ductus, which is usually obliterated, fixes the contiguous part of the aortic wall and may even appear to draw it toward the heart. Exceptions to this general type occur. The heart may be normal in every way; developmental anomalies other than bicuspid aortic valves are comparatively rare. Hypertrophy is present in about three fourths of the cases, but is associated in some of these with valvular disease, which may have caused the hypertrophy. The ascending aorta is often dilated to a varying degree and may be the seat of aneurysm, and sometimes there is an aneurysm distal to the stenosis; rupture is not infrequent. The aortic wall is at times thicker than normal, but usually is thinner. The inner surface may be normal, or it may show any degree of arteriosclerosis, sometimes with extensive calcification. Syphilitic change is infrequent. In some cases, there is slight gradual diminution of the caliber of the arch proximal to the lesion; in others, it remains unchanged up to the zone of stenosis. In a few instances, there appears to have been a double constriction. The degree of narrowing varies up to obliteration, and there is no characteristic picture of the inner aspect of the stenotic zone. When atresia is found, the intima lining the two blind sacs may appear normal; the occlusion may involve only the inner coats of the aorta, but more often the whole wall is apparently included. When a membranous wall stretches across the lumen, it may be perforated. The intima lining the sharply defined stricture may appear normal, but atheromatous change and even calcification, as well as scar tissue in the wall, have been found here. The descending aorta is often dilated just beyond the constriction, and it may return to its normal size distally; but more often it is somewhat smaller, probably on account of reduced blood pressure. In twenty cases, the whole aorta was hypoplastic. Just below the stenosis, there may be a variable degree of arteriosclerosis,

but more often the inner surface is clean. Bacterial endocarditis is common and sometimes associated with it is aortitis, which may be localized to the area of stenosis or just beyond. Except for aneurysms, especially of the cerebral arteries, which Turnbull [31] has shown are of developmental origin in nonsyphilitic young persons, other significant anomalies of the vascular system are rare, and defects of importance elsewhere even rarer.

A few cases of the infantile type have been reported in young children and even in older ones, but such subjects have usually been chronic invalids. The site of the stenosis has also been reported proximal to the ligamentum arteriosum in the instance of one robust adult.[32]

The collateral circulation is carried on chiefly through the anastomoses between branches of the subclavians and the aortic intercostals; the epigastric arteries sometimes contribute. Although the internal mammaries are of great importance as collateral channels and in some cases, notably those of Weber,[33] and Josefson,[34] seemed to have been the only dilated arteries, of others it has been remarked that they were not especially enlarged. Clinically, the enormous size of the artery along the vertebral border of each scapula is significant.

Microscopic study of the stenosed area itself has revealed little besides connective tissue. Reinitz [35] found the muscular and elastic layers of the aorta intact in two cases. The most thorough microscopic studies of the wall of the aorta have been made in cases of its rupture. Bronson and Sutherland,[36] Smith and Targett,[37] Bumke,[38] Oberndorfer,[39] Fränckel [40] (two cases), Sella [41] (two cases), Meixner [8] (four cases) and Binder [42] believe that diminution of elastica with replacement by

31. Turnbull, H. M.: Alterations in Arterial Structure and their Relations to Syphilis, Quart. J. Med. **8**:201, 1915.

32. Knierim, H. P.: Ein Fall von Stenose der Aorta in der Gegend der Insertion des ligamentum arteriosum, Marburg, 1880, p. 1.

33. Weber, F. P.: Stenosis (co-arctation) of the Aortic Isthmus, with Sudden Death from Rupture of a Cerebral Aneurysm, Proc. Roy. Soc. Med. (Sect. Med.) **20**:29 (June) 1927.

34. Josefson, A.: Stenos i isthmus aortae, Hygiea **3**:131, 1903.

35. Reinitz, O.: Ueber congenitale Stenose und Obliteration am Isthmus aortae, Kiel, Schmidt & Klaunig, 1908.

36. Bronson, E., and Sutherland, G. A.: Ruptured Aortic Aneurysms in Childhood, with the Report of a Case. Brit. J. Child. Dis. **15**:241, 1918.

37. Smith, F. J., and Targett, J. H.: Aneurysm of the Aorta in a Boy Aged Nine Years, Tr. Path. Soc. London **48**:53, 1896-1897.

38. Bumke, quoted by Meixner (footnote 8); by Abbott (footnote 29).

39. Oberndorfer, quoted by Meixner (footnote 8).

40. Fränckel, P.: Prapärate von spontanen Aortenrupturen, Berl. klin. Wchnschr. **1**:795, 1913.

41. Sella, quoted by Meixner (footnote 8) and by others.

42. Binder, A.: Zur Kasuistik der sogenannten Spontanenruptur der Aorta ascendens, Med. Klin. **15**:1091, 1919.

connective tissue is the essential feature. Oppenheim,[43] on the other hand, considered the aorta in his case essentially normal both grossly and histologically. Judging by experiments and observation at necropsies on aviators fallen from great heights, he believes that spontaneous rupture of a normal aorta may occur from a sudden increase in pressure in the region of the greatest stretching of the wall and of highest pressure, that is, of the under surface of the arch. These divergent views may be reconciled through the work of Turnbull,[31] who has found in the aortas of young persons without syphilis or abnormally high blood pressure occasional areas of focal degeneration in the media apparently originating in the rupture of the elastica. The initial break was presumably due to pressure, especially since such areas are found at the site of complete rupture independent of inflammation or degeneration. He believes the development of the aorta in such cases is relatively or absolutely insufficient.

Constriction of the aorta beyond the usual site has been reported by Schlesinger,[44] Quain,[45] Power [46] and Latile.[47] Roussy and L'Hermitte [48] have reported a case of thrombosis of the aorta distal to the renal arteries, which did not result fatally; the diagnosis was later corroborated at necropsy. Achard, Leblanc and Rouillard [49] found reports of only two such cases. The diagnosis in one case was purely clinical, and study of the original article suggests that it may have been coarctation; the other report was not available.

DIAGNOSIS

Coarctation of the infantile type has been diagnosed only once (in a child, aged 3).[50] It is of little practical importance that it should be diagnosed, since such patients are doomed to an early death. Coarctation of the adult type has been diagnosed clinically in four children.[51]

43. Oppenheim, Franz: Gibt es eine Spontanenruptur des gesunden Aorta und wie kommt sie zustande? München. med. Wchnschr. **45**:1234, 1918.

44. Schlesinger, quoted by Erman: Berl. klin. Wchnschr. **10**:217, 1873.

45. Quain, R.: Partial Contraction of the Abdominal Aorta, Tr. Path. Soc. London **1**:244, 1848-1850.

46. Power, quoted by Bonnet (footnote 28).

47. Latile: Athérome et oblitération partielle de l'aorte; bruit de galop, mort par asystolie, Bull. et mém. Soc. anat. de Paris **3**:40, 1878.

48. Roussy and l'Hermitte, quoted by Aubertin: M. Press & Circ. **124**:221, 1927.

49. Achard, C.; Lebanc, A., and Rouillard, J.: Trois cas d'oblitération de l'aorta, Bull. et mém. Soc. méd. d. hôp. de Paris **44**:903, 1920.

50. Carpenter, George: On Congenital Heart Affections, Especially in Relation to the Diagnosis of Various Malformations, Proc. Roy. Soc. Med. **2**:275, 1908-1909.

51. Carpenter (footnote 50). Ciaglinski, K.: Przypadek wrodzonego zwczenia aorty, Gaz. lek. **14**:740, 1894. Hochsinger, quoted by Bonnet (footnote 28); by Lommel: Med. Klin. **15**:892, 1919. Weigert, R.: Ueber einen Fall von angeborener Stenose der Aorta an der Einmündung des Ductus arteriosus Botalli, Allg. med. Centr.-Ztg. **74**:1, 1905.

In 1835 Legrand [52] and in 1839 Mercier [2] diagnosed an obstruction to the thoracic aorta, but Oppolzer [53] was the first to make a diagnosis of coarctation at the site of election; he did this twice and saw the diagnosis verified post mortem both times. Little or nothing has been added to Oppolzer's diagnostic criteria.

In the clinical diagnosis of coarctation, precordial murmurs are of little consequence, as they are sometimes absent; they may be caused by superimposed endocarditis, and, finally, they have been described in such a variety of terms that nothing pathognomonic can be deduced. The murmur in the interscapular space, more often to the left of the vertebral column, is of greater importance. Oppolzer attributed this to the stream of blood rushing through the greatly enlarged superior intercostal artery (intercostalis suprema); Walshe, according to Dickinson and Fenton,[20] attributed it to blood passing through the stenosed area, and thought that its absence would prove atresia. The data are insufficient to determine this point. A murmur in the same position may be caused by a patent ductus arteriosus, but distinguishing the two conditions, unless associated, should not cause trouble. The presence of enlarged superficial arteries of the neck and thorax (especially of the dorsal scapulars), over all of which bruits and thrills may be heard, is usually the outstanding feature. However, in 1920 Woltman and Shelden [54] diagnosed the condition on the basis of absence of pulsation in the abdominal aorta and femorals. More recently in one of his cases Laubry [55] verified post mortem the diagnosis made on such grounds; he believes that marked disproportion in the blood pressure of the brachial and femoral arteries is enough basis for the diagnosis. The blood pressure in the arm is often elevated, and in most cases the pulse pressure is also high. The electrocardiograph does not show any important or constant change, as Heynsius van den Berg,[56] King [1] and others have remarked. Roentgenologic examination of the thorax is of value in excluding aneurysm, which has been the most common erroneous diagnosis, but the presence of aneurysm does not exclude coarctation. The roentgenogram is also of some value in excluding intrathoracic neoplasm. However, I have been able to find but one case [57] in which such a tumor caused collateral

52. Legrand, quoted by Barié (footnote 4).

53. Oppolzer, quoted by Diesterweg (footnote 3); by Barié (footnote 4).

54. Woltman, H. W., and Shelden, W. D.: Neurologic Complications Associated with Congenital Stenosis of the Isthmus of the Aorta: a Case of Cerebral Aneurysm with Rupture and a Case of Intermittent Lameness Presumably Related to Stenosis of the Isthmus, Arch. Neurol. & Psychiat. **17**:303 (March) 1927.

55. Laubry, Charles: Discussion in Bull. et mém. Soc. méd. d. hôp. de Paris **50**:1725, 1926.

56. Van den Berg, M. R. H.: Stenosis Isthmi Aortae, Nederl. Tijdschr. v. Geneesk. **2**:773, 1911.

57. Seed, Lindon: Personal communication from the author.

circulation, and in one instance [9] of moderate stenosis a sarcoma of the mediastinum was associated. Loriga [19] advanced the original idea that exophthalmic goiter must be considered in the differential diagnosis on account of the bruits and thrills in the neck, but heretofore this point has not been emphasized.

When cardiac failure has been the most prominent factor, coarctation has been thought of a few times but discarded because evidence of collateral circulation was not found; however in most of these cases, aortic aneurysm has been diagnosed. In a number of instances, subacute bacterial endocarditis has overshadowed the picture. Some persons with this abnormity have died suddenly or from causes not related to the cardiovascular system.

COARCTATION DIAGNOSED DURING LIFE

The clinical diagnosis of coarctation has been reported twenty-two times according to Barié,[4] Bonnet,[28] Hirschfelder,[58] Meixner [8] and King.[1] In addition, the following authors have reported the clinical diagnosis of coarctation on thoroughly adequate grounds: Babonneix, Oury and Widiez,[59] S. D. Blackford,[60] Brown,[61] Deneke,[62] Edelmann and Maron,[30] van den Berg,[56] King (five cases),[63] Kövesi [64] in addition to the case examined at necropsy), Laboulbène and Claisse,[65] Laubry [55] (two cases), Lommel,[66] Oppenheimer,[67] Parsons-Smith,[68] Pel,[69] Pilod and Hugonot,[70] Reichel,[71] Schlesinger,[27] Starling,[72] Sturs-

58. Hirschfelder, A. D.: Diseases of the Heart and Aorta, Philadelphia, J. B. Lippincott Company, 1918, p. 556.

59. Babonneix, L., Oury and Widiez: Rétrécissement congénital de l'aorte et syndrome hémogénique, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:866 (June 16) 1927.

60. Blackford, S. D.: Personal demonstration.

61. Brown, Alexander: Congenital Stenosis of the Aorta, Lancet **1**:1719, 1912.

62. Deneke, Theodor: Zur Klinik der Isthmusstenose der Aorta, Virchows Arch. f. path. Anat. **254**:336, 1925.

63. King, J. T., Jr.: Clinical Aspects of Congenital Anomalies of the Aorta, Am. Heart J. **2**:144 (July) 1926; also footnote 1.

64. Kövesi, G.: Stenosis Isthmus Aortae, Orvosi hetil. **1**:1055, 1906.

65. Laboulbène, A., and Claisse, P.: Rétrécissement congénital de l'aorte descendante, à sa partie supérieure, vers l'abouchement du canal artériel, Bull. et mém. Soc. méd. d hôp. de Paris **7**:945, 1890.

66. Lommel, F.: Ueber Stenose des Aortenisthmus, Med. Klin. **15**:892, 1919.

67. Oppenheimer, B. S.: Personal communication from the author.

68. Parsons-Smith, B. T.: Case of Congenital Aortic Atresia, Proc. Roy. Soc. Med. **14**:73, 1921.

69. Pel: Isthmus stenose, Nederl. Tijdschr. v. Geneesk. **1**:2032, 1908.

70. Pilod and Hugonot: Double rétrécissement congénital de l'aorte à son origine et au niveau de l'isthme, Bull. et mém. Soc. méd. d. hôp. de Paris **1**:1719, 1926.

berg,[73] Langmead, Weber and Gossage,[74] Weber and Price[75] and Werley.[76] Coarctation has therefore been believed to be present, although not verified by necropsy, at least fifty times. Pilod and Hugonot did not find evidence of collateral circulation over the thorax. In the case reported by Weber and Price, the patient died from external rupture of an aneurysm of the right subclavian artery. A definite history of intermittent claudication was given in Heynsius van den Berg's case, and in one of King's; Parsons-Smith's patient had "a functional incapacity of the lower limbs, especially noticeable after resting." Cramps in the legs were not common.[76] Edelmann and Maron's patient had muscular arms but poorly developed legs. Some hypertrophy of the heart was found roentgenologically in five cases;[77] roentgenologic examination of the heart was negative in five.[78] The electrocardiogram was essentially negative in eight cases.[79] The stenosis was considered proximal to the origin of the left subclavian artery by Brown, Deneke and Stursberg. Coarctation has been definitely diagnosed in life and verified post mortem nineteen times;[80] a tentative diagnosis was made twice,[81] and an obstruction of the thoracic aorta was diagnosed six times.[82]

---

71. Reichel, O.: Ein Fall von Isthmusstenose der Aorta, Allg. Wien. med. Ztg. **46**:268, 1901.

72. Starling, H. J.: Coarctation of the Aorta, Lancet **1**:1317, 1920.

73. Stursberg, H.: Sphygmographische Befunde bei Verengerung der Aorta am Isthmus, Deutsches Arch. f. klin. Med. **107**:33, 1912.

74. Langmead, Frederick: A Case of Thoracic Aneurysm Not Connected with the Aorta, Proc. Roy. Soc. Med. **5**:194, 1912; discussion by F. P. Weber. Gossage, A. M.: Case of Coarctation of the Aorta, Proc. Roy. Soc. Med. **6**:1, 1912.

75. Weber, F. P., and Price, F. W.: Coarctation of the Aorta in an Adult with Death Due to Rupture of an Aneurysm in the Neck, Lancet **2**:692, 1912.

76. Werley, G.: Aortic Hypoplasia and Isthmus Stenosis: Case Reports, Texas State J. Med. **23**:285 (Aug.) 1927.

77. Deneke (footnote 62). Edelmann and Maron (footnote 30, first reference). Van den Berg (footnote 56). King (footnote 63). Pilod and Hugonot (footnote 70).

78. King (footnote 1). Starling (footnote 72). Werley (footnote 76).

79. Deneke (footnote 62). Van den Berg (footnote 56). King (footnotes 1 and 63). Parsons-Smith (footnote 68). Pilod and Hugonot (footnote 70).

80. Abbott (footnote 29). Bahn, Karl: Ueber isolierte Dextrocardie mit Isthmusstenose der Aorta und Endocarditis lenta, Deutsches Arch. f. klin. Med. **166**:297 (March) 1925. Barié (footnote 4). Bonnet (footnote 28). Gossage, A. M.: Coarctation of the Aorta, Proc. Roy. Soc. Med. **2**:210, 1909. Laubry (footnote 55). Maixner, Emerich: Vrozené súžení srdečnice poblíže provodu Bottalova. Súženi otvoru tepenného levého; nedomykavost chlopní měsíčitých aorty a dvojípové, Čas. lék. česk. **17**:201, 209, 1878. Umber: Aortenstenose und Isthmusenge der Aorta, München. med. Wchnschr. **53**:96, 1906. Weinberger, Maximilian: Isthmusstenose der Aorta, kombiniert mit offenen Foramen ovale, Deutsche. med. Wchnschr. **35**:512, 1909; Weitere Beiträge zur Radiographie der Brustorgane, Med. Klin. **4**:584, 1908.

CASES OF COARCTATION AS FOUND IN THE INFANT AT NECROPSY

This series, which does not include reports abstracted by Barié, Bonnet, or Abbott may be presented most conveniently in two groups:

Group 1 includes uncomplicated examples of the infantile type, in which the aorta is narrowed between the origin of the left subclavian and the mouth of the ductus arteriosus; the ductus is patent and supplies varying amounts of blood to the descending aorta. Cases have been reported by: Audry,[83] Borissowa,[84] Carpenter (two cases),[85] Cautley,[86] Essard,[87] Gibert,[88] Hoche and Morlot,[89] Holt,[90] Kolisko,[91] Meixner,[8] Morlot and Vermelin,[92] Nagel,[93] Sankott[94] and Strassmann[95] (two cases). One subject died[84] from diphtheria at the age of 18 months, another from[94] bacterial endocarditis at 3 years; the remaining thirteen died in less than one year, bronchopneumonia being the terminal event in six. In six cases, the family history was said not to be significant, and the infant was born at full term. Cyanosis was mentioned as present in three cases and absent in six. Imperfect closure of the interauricular

81. Josefson (footnote 34). Knierim (footnote 32).

82. Abbott, M. E.: Coarctation of the Aorta, Am. Heart J., to be published.

83. Audry, J.: Rétrécissement de l'isthme de l'aorte chez un nouveau-né, Lyon med. **106**:161, 1906.

84. Borissowa, A. P.: Zwei Fälle von Stenosis isthmi aortae, Medizinskoje Obozrenige, lxxiv, no. 13; abstr., Zentralbl. f. allg. Path. u. path. Anat. **22**:379, 1911.

85. Carpenter, George: Three Cases of Congenital Heart Disease, Brit. J. Child. Dis. **5**:396, 1908.

86. Cautley, E.: Two Specimens of Congenital Heart Disease. (1) Stenosis of the Isthmus Aortae with Patent Ductus Arteriosus and Patent Interventricular Septum, Proc. Roy. Soc. Med. **2**:34, 1908-1909.

87. Essard: Malformation congénitale de l'aorte, Lyon méd. **108**:1034, 1907.

88. Gibert: Distribution anormale des artères aorte et pulmonaire, Bull. et mém. Soc. anat. de Paris **14**:203, 1839.

89. Hoche, L., and Morlot, R.: Un cas de sténose congénitale de l'aorte chez un nouveau-né, Bull. et mém. Soc. anat. de Paris **91**:91, 1921.

90. Holt, L. E.: Malformation of the Heart; Open Foramen Ovale and Ductus Arteriosus; Stenosis of Aorta; Hypertrophy of Both Ventricles, New York M. J. **39**:335, 1884.

91. Kolisko, quoted by Meixner (footnote 8); by Woltman and Shelden (footnote 54). Abbott (footnote 82).

92. Morlot, R., and Vermelin, H.: Deux cas de sténose congénitale de l'aorte chez le nouveau-né, Compt. rend. Soc. de biol. **85**:1082, 1921.

93. Nagel, W.: Ein Beitrag zur Kasuistik über angeborene Herzfehler, Freiburg, Speyer and Kaerner, 1908.

94. Sankott, A.: Ueber einen eigenartigen Fall von Stenose des Isthmus aortae, Anat. Anz. **48**:261-273, 1915.

95. Strassmann, G.: Der plötzliche Tod bei Stenose des Isthmus aortae, Beitr. z. gerichtl. Med. **5**:91, 1922.

septum was found seven times, of the interventricular septum four times. In eleven cases, the right ventricle was hypertrophied; in six, the left ventricle.

Group 2 includes atypical examples in infants. Cases have been reported by Barrett,[96] Diesterweg,[3] Dreyfuss[97] (four cases), Fisher[98] Greenfield,[99] Grieg,[100] Fränckel,[40] von Hofsten,[101] Hayashi,[102] Herxheimer,[103] Marx,[104] Meixner[8] (two cases), Pamard,[105] Saltykow,[106] Sieber,[107] Steidele,[108] Stille,[109] Sternberg,[110] Vallette and Mollaret,[111] Verocay,[112] Volbeding[113] and Waggaman.[114] The most striking fact about this group of twenty-six atypical cases is the presence of grave developmental defects not connected with the cardiovascular anomalies in eight cases,[115] and severe cardiovascular anomalies in two of these[116]

96. Barrett, T. B.: Malformation of a Foetus, Lancet **23**:349, 1835.

97. Dreyfuss, M.: Coarctation of the Aorta, Infantile Type, Internat. A. M. Museums Bull., to be published.

98. Fisher, Theodore: Two Cases of Congenital Disease of the Left Side of the Heart, Brit. M. J. **1**:639, 1902.

99. Greenfield, quoted by Humphrey: Congenital Diseases of the Heart, in Allbutt and Rolleston; System of Medicine, New York, The Macmillan Company, 1909, p. 286.

100. Grieg, quoted by Kohl: Centralbl. f. allg. Pathol. u. path. Anat. **20**:1089, 1909.

101. Von Hofsten, S.: Fall af Aortastenose, Hygiea **48**:19, 1886.

102. Hayashi, A.: Stauungslunge bei Offenbleiben des Ductus Botalli, Monatschr. f. Kinderh. **11**:224, 1912.

103. Herxheimer: Discussion on Stenose des Aortenbogens vor Einmündung des Ductus Botalli, Verhandl. d. deutsch. path. Gesellsch. **13**:205, 1909.

104. Marx, Herman: Ueber einen Fall von zunehmender Stenose der Aorta vom Conus bis zur Einmündung in dem Ductus Botalli, Worms-am-Rhein, A. K. Boeninger, 1912.

105. Pamard, quoted by Kohl (footnote 100).

106. Saltykow, quoted by Kohl (footnote 100).

107. Sieber: Demonstration von embryonalen Missbildungen am Zirkulations- und am Diegestionsapparate, Deutsche med. Wchnschr. **35**:692, 1909.

108. Steidele, quoted by Kohl (footnote 100).

109. Stille, quoted by Hirschfelder (footnote 58); by Kohl (footnote 100).

110. Sternberg-Brunn, Carl: Beiträge zur Kenntniss der angeborenen Herzfehler, Verhandl. d. deutsch. path. Gesellsch. **13**:198, 1909.

111. Vallette, P., and Mollaret, J.: Un cas de rétrécissement congénital de l'aorte chez un nourisson, Marsellie méd. **42**:41, 1906.

112. Verocay, Jose: Contributo alla casistica dell' artresia congenita dell' aorta in prossmità del dutto arterioso del Botallo, Pathologic. **5**:35, 1913.

113. Volbeding, quoted by Verocay (footnote 112).

114. Waggaman: Congenital Stenosis of the Aorta, Tr. Med. Soc. Dist. Columbia **3**:65, 1876.

115. Barrett (footnote 96). Dreyfuss (footnote 97). Meixner (footnote 8). Sieber (footnote 107). Sternberg (footnote 110). Verocay (footnote 112).

116. Dreyfuss (footnote 97). Sieber (footnote 107).

and in two others.[117] Three of the subjects were stillborn and a fourth was aborted. In four cases,[118] and perhaps a fifth,[40] the constriction was distal to the mouth of the obliterated ductus arteriosus, that is, of the adult type; one of these 3 subjects was but 8 days of age. The right ventricle was hypertrophied in nine cases, the left in six. The interauricular septum was imperfect in at least seven cases, the interventricular in four.

Comment on Groups 1 and 2.—To the series of eighty-two cases of coarctation in infants reviewed by Abbott,[29] the present series of forty-two is added. In this group, there are seventeen males and sixteen females; in nine, the sex was not specified. These figures agree with Manneberg's [119] denial of the predominance in males. The oldest subject was 3 years of age; only one other was more than 1 year; Abbott included none older than 1 year. In sixteen cases the true anatomic isthmus was narrowed, and there was no abnormity of note except in the heart; these were classical and uncomplicated examples of the infantile type. The adult type was found in four cases and probably was not related to the cause of death. The prolongation of the ductus arteriosus formed the descending aorta in nine cases; twenty-five were previously assembled. Other cardiovascular defects were found in twenty necropsies.

CASES OF COARCTATION AS FOUND IN THE ADULT AT NECROPSY

This series,[120] which also does not include reports abstracted by Barié, Bonnet or Abbott [29] (in "Modern Medicine"), may be presented in groups.

Group 1.—In this group are classical examples of the adult type (without complications) in which constriction is at or distal to the mouth of the ductus arteriosus. Cases have been reported by Bartels,[17] Beneke,[121] Broome,[122] Edgren,[123] Halberer,[124] Hansteen [9] (three cases),

117. Fisher (footnote 98). Stille (footnote 109).

118. Diesterweg (footnote 3). Greenfield (footnote 99). Von Hofsten (footnote 101). Waggaman (footnote 114).

119. Manneberg, quoted by Reinitz (footnote 35).

120. Dr. Abbott, in her paper now in press (Abbott, M. E.: Coarctation of the Aorta, Am. Heart J., to be published) is including forty cases in this series, and a previously published case from the Mayo Clinic, from her own studies and seventeen cases from my abstracts, as well as six cases (Hinrichsmeyer, Libman, Nieuwejaar, Oehl, Taruffi and Wadstein) found by her in the literature since this paper was completed.

121. Beneke: Endokarditis lenta mit Isthmusstenose, München. med. Wchnschr. **69**:413, 1922.

122. Broome, H. H.: A Dissection Showing Abnormalities of the Veins, the Arteries and the Kidneys, Proc. Anat. Soc. Great Britain and Ireland **35**:53, 1900-1901.

Harrison,[125] Hart [126] (two cases), Josefson,[34] Kolisko,[91] Laubry,[55] Lützow-Holm,[127] Maixner,[80] Mackenzie,[128] Murray,[129] Reinitz,[35] Santas,[130] Strassmann [95] and Zeoni.[24]

One subject [123] in this group had suffered from cardiac symptoms for twelve years, but had been incapacitated for only four weeks; four others [131] had suffered from cardiac symptoms for more than a year. Otherwise their previous health had been good; it may be emphasized that one [126] was an air-pilot in the German army, although coarctation in this case was extreme. Josefson was of the opinion that his patient was afflicted with coarctation, but since he was unable to find pulsating superficial arteries during life, he hesitated to make a definite diagnosis; at necropsy, it was found that the internal mammary arteries provided the principal collateral channels. A similar case [132] belongs in another group. Murray, Santas and Zenoni presented clinical observations sufficient for the diagnosis of coarctation, but diagnosed aneurysm of the thoracic aorta.

Haberer has reported a case of unusual interest. Three days before admission to the hospital the patient developed transverse myelitis; this caused death through complications three months later. The most striking observation at necropsy was that the anterior spinal artery had contributed to the collateral circulation and caused compression of the spinal cord at the level of the second dorsal nerves. In spite of atresia of the aorta, this woman had borne seven children. Of the women in whom atresia has been found, one died at the birth of her ninth child,[6] and another was survived by seven children.[95] In one case in which the

123. Edgren, J. G.: Fall af isthmusstenose med relative aortainsufficiens, Nord. med. Ark., Festband, 1897, p. 27.

124. Haberer, H.: Ein Fall von seltenen Collateralkreislauf bei angeborener Obliteration der Aorta und dessen Folgen, Ztschr. f. Heilk. **24**:26, 1903.

125. Harrison, T. J.: Singular Abnormality of the Arterial System; Constriction and Obliteration of the Aorta, etc., Penins. M. J. **3**:514, 1855-1856.

126. Hart, C.: Ueber die totale Obliteration des Aortenisthmus, Med. Klin. **16**:1337, 1920.

127. Lützow-Holm, G.: Svaer medfedt stenose i isthmus aortae, pendselig dod, Norsk Mag. f. Laegevidensk. **85**:1066 (Oct.) 1925.

128. Mackenzie, G. M.: Coarctation of the Aorta with Staphylococcus Endocarditis, Am. J. M. Sc. **174**:87, 1927.

129. Murray, G. R.: A Case with Comments: A Case of Incomplete Coarctation of the Aorta; Necropsy, Practitioner. **72**:284, 1900.

130. Santas, M. A.: Estenosis congénita del istmo de la aorta en un individuo de 61 años, Rev. Soc. méd. argent. **14**:17, 1906.

131. Lützow-Holm (footnote 127). Murray (footnote 129). Santas (footnote 130).

132. Erdmenger, Rudolf: Zwei Fälle von angeborenen Herzfehler mit Sektionsbefund (Pulmonalstenose bezw. Isthmusstenose), Götting., L. Hofer, 1912.

stenosis was all but complete, the patient died near the end of her second pregnancy.[95] Of the women in whose cases coarctation was diagnosed clinically, one had had four children,[56] one eleven[75] and a third fourteen.[74]

Strassmann[95] seems to have reported the one case in which thyroidectomy had been performed; this was probably for adenomatous goiter.

Group 2.—This group includes examples of coarctation in which death was due to rupture of the aorta. Cases have been reported by Berger,[133] Bumke,[38] Kolisko,[91] Trevor,[134] Binder,[42] Bronson and Sutherland,[36] Fränckel (two cases),[40] Horder,[135] Meixner,[8] Oppenheim,[43] Staunig,[136] Strassmann (four cases),[95] Smith and Targett,[37] Turnbull[31] and West.[137]

In two cases rupture occurred through an aneurysm which was the site of vegetations; Abbott[29] cites a similar one, reported by Smith and Hausmann. The seventeen cases of spontaneous rupture of the aorta associated with coarctation reviewed here bring the total to thirty-eight;[138] of these, thirty-one patients were men and four women; most of them were from 17 to 33 years of age. Meixner attributes the striking prevalence of death from this cause in muscular males during the age of greatest effort to unusually high blood pressure produced by their energetic life or to a congenital weakness of the walls of the aorta (as Turnbull[31] does), or more probably to a combination of these two factors. In seven of these seventeen cases, it is noted that the initial symptoms appeared during or after prolonged violent exercise; death followed at once when the first break in the aortic wall was complete, or a few hours later when it became so. The fact that in one[135] case the stenosis was slight and in another[42] only moderate, lends support to the belief that the rupture was due essentially to imperfect development of the wall of the aorta. In eight of this group, the ascending aorta was dilated and thin-walled, and in five[139] definite aneurysm was found. Attention may

133. Berger, quoted by Meixner (footnote 8).

134. Trevor, quoted by Humphrey: Congenital Diseases of the Heart, in Allbutt and Rolleston, System of Medicine, ed. 2, New York, The Macmillan Company **6**:286, 1909.

135. Horder, T. J.: Dissecting Aneurism of the Aorta in a Boy Aged Twelve; Rupture into Pericardium, St. Barth. Hosp. Rep. **43**:57, 1907.

136. Staunig: Aortenruptur, Berl. klin. Wchnschr. **50**:469, 1913.

137. West: False Aneurism with Obliteration Probably Congenital of the Aorta, Tr. Coll. Phys., Philadelphia **2**:194, 1848.

138. Abbott's new series includes cases of two young men, reported by Nieuwejaar, and Wadstein, which make the total forty; in both, the aortic valve was bicuspid.

139. Binder (footnote 42). Bronson and Sutherland (footnote 36). Horder (footnote 135). Kolisko (footnote 91). West (footnote 137).

also be called to the disproportion between the size and development of the upper and lower parts of the body in the case reported by West. A similar disproportion has been recorded twice,[29] as well as in a clinical report by Edelmann and Maron.[30]

Group 3.—Examples of coarctation in which death was due to cerebral hemorrhage are included in this group. Cases have been reported by Bahn,[80] Borissowa,[84] Erdmenger,[132] Kolisko,[91] Koster and Forselius,[30] Strassmann [95] and Weber.[140]

Borissowa's patient was a sickly child, and in this case, aortic stenosis and coarctation were present, both in an extreme degree, but above the narrowed ostium, the ascending aorta was dilated. Erdmenger's patient had suffered from mitral stenosis of rheumatic origin. Koster and Forselius' patient was syphilitic. The others of this group were healthy and robust prior to death. Definite ruptured aneurysm was mentioned by Kolisko, Strassmann and Weber. Bahn's case, which was correctly diagnosed in life, has no fellow. The electrocargiogram was negative except for inverted T-waves in leads 1 and 2. At necropsy, the heart was proved to be on the right side, but the chambers were in their normal relative positions, and the arch of the aorta was to the left. Inversion of other viscera was not noted. Bacterial endocarditis was also observed in this case, but the hemorrhage was independent of it. Josefson's [34] patient also suffered from endocarditis, but he died from cerebral hemorrhage secondary to embolus to the brain.

Group 4.—The cases in this group are atypical example of coarctation. Cases have been reported by Knierim,[32] Kohn,[141] Kövesi,[64] Kurcyusza,[142] Lantinga,[143] Lesseliers,[144] Umber [80] and Weidman.[145]

Knierim reported atresia proximal to the obliterated ductus, but did not emphasize this unique observation; the possibility of an error may therefore be considered. His patient was a robust middle-aged man. Kohn's case, that of a man aged 57, did not present any characteristics of coarctation either clinically or at necropsy, except "marked stenosis of the isthmus with atheroma." Four other examples of [146] coarctation

140. Weber (footnote 33).

141. Kohn, Albert: A Case of Dilatation of the Aorta Due to Constriction at the Isthmus, M. Rec. **79**:652, 1911.

142. Kurcyusza, A.: Insufficientia totius aortae congenita; stenosis arcus aortae, endocarditis atheromatosa, Gaz. lek. **16**:81, 1874.

143. Lantinga, Freerk: Over vernauwing der aorta, Groningen, J. B. Wolters, 1874.

144. Lesseliers, L.: Cas remarquable de rétrécissement de la crosse de l'aorte, Ann. Soc. de méd. de Gand **60**:45, 1882.

145. Weidman, F. D.: Congenital Stenosis (Coarctation) of the Isthmus of the Aorta, Proc. Path. Soc. Phila. **16**:78, 1914.

146. Hansteen (footnote 9). Kurcyusza (footnote 142). Lantinga (footnote 143). Lesseliers (footnote 144).

in which collaterals were distinctly said to be absent are included in this series; the narrowing in three of these was moderate, and in two, generalized hypoplasia of the aorta was associated. Three cases without evidence of collateral circulation at necropsy occur in Abbott's [29] series. Two patients [147] in this group had suffered from cardiac symptoms since birth and two others [148] for about a year. The aorta was hypoplastic throughout in five cases; [149] Abbott reviewed nineteen such cases in her 1927 monograph. In the literature, general hypoplasia of the aorta is less common than coarctation.

Comment on Groups 1 to 4.—This series consists of fifty-seven cases in which the age was more than 3 years and in which the data are more or less adequate for statistical study. Manneberg [119] has denied that coarctation actually occurs more often in men than in women, and explains the apparent discrepancy by the greater number of necropsies performed on men; he estimates the ratio as 2:1. Abbott [82] reports cases in ninety-two males and thirty-nine females, which is in harmony with this theory; but in this additional group of fifty-seven, there were forty-seven cases in men and eight in women, which is more in keeping with the traditional view that coarctation is more common in males. In my group, eight were aged from 11 to 15 years, five from 16 to 20, fourteen from 21 to 30, and eleven from 31 to 40, as compared with four, twenty-three, thirty-two and twenty-five in the same age periods in Abbott's group. Of the fifty-seven cases reviewed by me, the aorta was obliterated in fifteen, extremely stenosed in twenty-nine, moderately stenosed in ten and slightly stenosed in one; the degree of stenosis was not given in two. That is, of 194 cases of the combined series (Abbott's revised series and mine), the diameter of the lumen of the aorta was less than 6 mm. at the site of coarctation in 151 cases. In my series, collateral circulation was said to be present in thirty-five, and not mentioned in fifteen, although it was implied in about half of these. In five cases of moderate stenosis, collateral circulation was said to be absent. The heart was enlarged in forty-four of these fifty-seven cases and not enlarged in six; among the latter, there were two cases of atresia,[150] two of extreme stenosis,[151] in one [143] of which collaterals were said to be absent, and two [152] of moderate degree. The ductus was patent in five cases, bringing the total of such cases to seventeen. Bicuspid aortic valve

147. Kurcyuza (footnote 142). Lantinga (footnote 143).

148. Knierim (footnote 32). Umber (footnote 80, eighth reference).

149. Kovesi (footnote 64). Kurcyusza (footnote 142). Lantinga (footnote 143). Umber (footnote 80). Weidman (footnote 145).

150. Franckel (footnote 40). Harrison (footnote 125).

151. Lantinga (footnote 143). Smith and Targett (footnote 37).

152. Hansteen (footnote 9). Horder (footnote 135).

was present in fourteen instances; thirty-one were previously reviewed.[82] In my series, cerebral hemorrhage was found eight times; in three, rupture of an aneurysm was specified. Simple hemorrhage is reported seven times, ruptured aneurysm three times and clinical evidence of cerebral hemorrhage six times in Abbott's latest review. Knierim [32] reported an unruptured aneurysm of the basilar artery. In most cases the brain was not examined post mortem, or perhaps cerebral aneurysm would have been recorded more often.[54] The obvious explanation of the affection of the arteries of the brain would appear to be high blood pressure in the proximal aorta. The efficiency of the internal carotid arteries in young persons, however, probably prevents high pressure in the cerebral arteries, and this argument strengthens Turnbull's [31] hypothesis that these aneurysms are rather due to inherent weakness of the arterial wall. The incidence of aortic aneurysm has been mentioned. Aneurysms of the left brachial in a boy and of the left verebral have been reviewed.[54] In my series, death was due to cardiac failure in sixteen cases, making a total of eighty-four deaths due to this cause. Subacute bacterial endocarditis was responsible for death in six cases in this series; in two, it was complicated with bacterial aortitis; endocarditis was present in another case, and in two others, if infection did not cause aortic aneurysm, at least infection led to rupture of the aneurysm. Minor vascular anomalies, such as persistent left superior vena cava,[153] origin of the vertebral artery from the arch [154] and patent interauricular septum [155] were found in five cases in addition to the five examples of generalized aortic hypoplasia. Developmental defects of consequence were found elsewhere in two cases [156] and minor ones in two others.[157]

Group 5.—Miscellaneous examples of coarctation are given in this classification. Moriani [158] has published a case that he likened to one of Mönckeberg's;[22] the original article is not available to me. Weinberger [80] demonstrated a postmortem specimen with a patent foramen ovale, which is presumably from the case reported by him clinically the preceding year. Jaffé and Sternberg [7] refer to an example in a soldier dying of pulmonary tuberculosis. Reports of sixteen other apparently genuine cases without adequate details have been found. Eleven of these were in infants, and in four of the five adult cases it was noted that coarctation was not marked and without clinical significance.

---

153. Broome (footnote 122). Kolisko (footnote 91).

154. Haberer (footnote 124). Kolisko (footnote 91).

155. Bronson and Sutherland (footnote 36). Kohn (footnote 141).

156. Bronson and Sutherland (footnote 36). Reinitz (footnote 35).

157. Broome (footnote 122). Lützow-Holm (footnote 127).

158. Moriani, G.: Contributi alla patologia vasale; complicazioni valvulari aortiche in stenosi congenita dell' istmo; abstr. Pathologia. **3**:241, 1911.

Anders,[159] Langwill,[160] and Kurtz, Sprague and White[161] have reported cases of moderate coarctation in which other cardiac lesions appeared to be of greater importance. In her current publication, Abbott[82] is excluding nineteen cases of this type from her 1927 article and adding thirteen others. In fourteen of these thirty-five cases, grave developmental defects were associated with moderate coarctation, and slight coarctation complicated other minor cardiovascular anomalies in twenty-one. In fourteen instances, the ductus arteriosus was widely patent. Some of this series were complicated examples of the infantile type; four of these subjects were less than 5 years of age, but others were older. These thirty-five cases are probably not all of those published in which some degree of coarctation has been overshadowed by more serious conditions. Abbott discusses the subject in more detail in her current work and appends a bibliography.

AN UNPUBLISHED CASE OF COARCTATION WITH NECROPSY

Dr. Walter D. Shelden[162] has permitted me to report a case diagnosed by him in 1906 (fig. 2). A man, aged 44, in the terminal stages of gastric carcinoma, was referred on account of an unusual cardiovascular condition. During the preceding nine months, he had suffered from cramps in the legs, which lasted a few minutes two or three times at night; he had become dizzy and had complained of palpitation and pain in the chest on exertion. He had been growing weaker, especially in the legs. The carotid arteries were markedly thickened and pulsating forcibly. Pulsation in the abdominal aorta, although the parietes were thin and relaxed, could not be felt; in the femorals it was weak and often imperceptible. The dorsal scapular arteries were tortuous and distended, and near the angle of the scapula were larger than the radial. They anastomosed with a knot of vessels near the spine. In the posterior part of the left axilla, a large artery was found in which blood was flowing downward; one branch disappeared in the ninth interspace and the other extended toward the angle of the scapula and was lost in the seventh or eighth interspace. Pressure on the left brachial stopped pulsation in both branches. Cardiac dulness was not increased. At the base, a soft blowing systolic murmur remarkable for its diffuse character was heard; this was perhaps most marked over the aortic area, but it was almost equally intense in the back to the left of the vertebral column above the level of the spine of the scapula. Atresia of the aorta just beyond the obliterated ductus was found at necropsy.

---

159. Anders, J. M.: Sudden Death in Aortic Stenosis with Report of Two Cases, One Complicated with an Aneurismatic-Like Dilatation of the Aorta at Its Root and Marked Stenosis of this Vessel Beyond the Dilatation, Med. News **80**:872, 1902.

160. Langwill, H. G.: An Unusual Cardiac Case, Scot. M. & S. J. **1**:723, 1897.

161. Kurtz, C. M.; Sprague, H. B., and White, P. D.: Congenital Heart Disease: Interventricular Septal Defects with Associated Anomalies in a Series of Three Cases Examined Postmortem, and a Living Patient Fifty-Eight Years Old with Cyanosis and Clubbing of the Fingers, Am. Heart J. **3**:79 (Oct.) 1927.

162. Shelden, W. D.: Personal communication to the author.

CASES OF COARCTATION AT THE MAYO CLINIC DIAGNOSED CLINICALLY

CASE 1.[163]—In the first case so diagnosed, the patient was a woman, aged 44, who after walking suffered from precordial pressure, dyspnea, tachycardia, vertigo, occasional vomiting and intermittent claudication. Pulsation in the subclavian

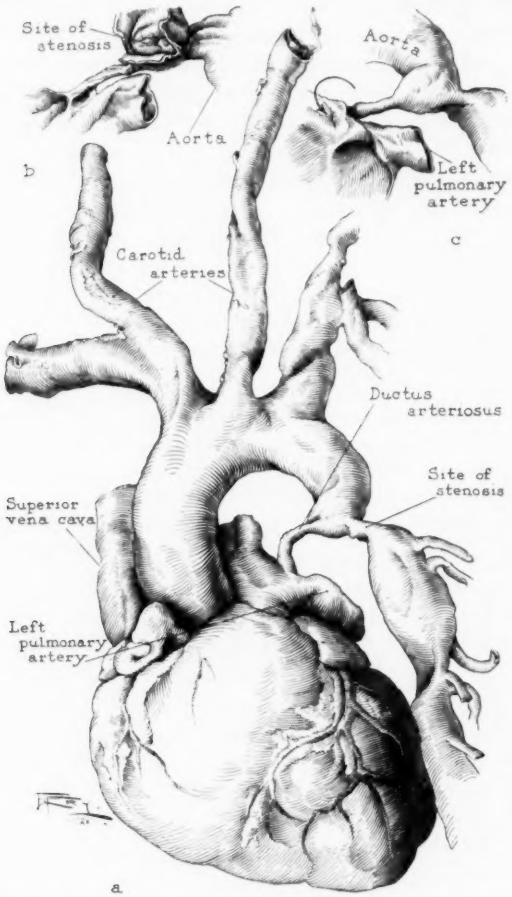

Fig. 2.—The heart and aorta from Shelden's case, drawn from the original specimen.

and carotid arteries was strong, but other dilated arteries were not visible or palpable over the thorax. In contrast to the multiparas who have been cited, this woman had lost two premature infants, and perhaps had had an early miscarriage. When last heard from, her condition was unchanged.

163. Previously reported by Woltman and Shelden (footnote 54).

Comment.—In one other case [70] diagnosed clinically, and in several diagnosed at necropsy [164] in which the diagnosis of coarctation was considered during life, no evidence of superficial collateral circulation was found, but postmortem examination revealed marked enlargement of the intrathoracic arteries. Laubry [55] emphasizes that pronounced disproportion of the brachial and femoral blood pressure is a sufficient basis for the diagnosis.

Case 2.[165]—A robust, athletic youth, aged 20, had been in coma two days at the time of admission to the hospital. Necropsy examination confirmed the clinical diagnosis of obliteration of the aorta in the region of the insertion of the ligamentum arteriosum involving the origin of the left subclavian and hemorrhage at the base of the brain. This hemorrhage came from the rupture of a large aneurysm at the juncture of the posterior communicating and middle cerebral arteries. The heart was moderately hypertrophied and the aortic valve presented but two cusps.

Case 3.—A farmer, aged 30, was admitted to the clinic on July 31, 1925. He gave a history of a rather sudden onset of dyspnea ten weeks previously. Two weeks after the onset of the dyspnea, edema of the ankles was noticed, but it disappeared later with rest. There was no history of weakness or coolness of the legs, claudication or headache. A systolic murmur followed by a reduplicated and accentuated second sound in the second right interspace and a rough systolic murmur over the apex were heard. The physical signs of coarctation were present. Hemorrhage or exudate were not noted in the fundus. Although a moderate amount of albumin, erythrocytes and leukocytes were present in the urine, the result of the phenolsulphonphthalein test was 65 per cent and the blood urea 24 and 16 mg. for each hundred cubic centimeters on different days. The patient was given the dietary regimen for nephrosis and advised to give up farm work for a sedentary occupation. In February, 1927, he wrote: "Am feeling fine now. Have a lot of work and expect to do it all myself."

Comment.—The chief point of interest in this case is that the association of high blood pressure and a high grade of albuminuria involved the differential diagnosis of glomerulonephritis and nephrosis.

Case 4.—A boy came to the Mayo Clinic on Aug. 17, 1926, for advice concerning his heart.[164] Ten months previously, during the routine examination of candidates for the football team at his high school, "high blood pressure and leakage of the heart" were diagnosed, and he was placed on a rather strict regimen. He had felt so well that he wished to know if it were necessary to continue this life of restricted activity. Prior to October, 1925, besides doing his share of the farm work, he had been playing football, baseball and basketball with some local distinction. He had never noticed cyanosis, tinnitus, vertigo, headache, or pain, aching or weakness in the legs, but he had observed that his feet easily became cold. A harsh systolic murmur over the precordium, most intense in the second left interspace, was transmitted to the vessels of the neck. A diastolic murmur was not present in the aortic area, but one was audible along the upper part of the left border of the sternum; its character was not altered by change of position. Although there was no Corrigan or capillary pulse, the blood pressure sug-

164. Blackford, L. M.: Coarctation of the Aorta, Proc. Weekly Staff Meetings Mayo Clinic **1**:103, 1926; **2**:281, 1927.

gested aortic regurgitation. In attempting to elicit the "pistol-shot in the groin," it was observed that pulsation in the femoral artery was faint and less pronounced than in the inferior epigastric and superficial circumflex iliac arteries. The patient was urged to abandon his athletic career and to prepare himself to earn a living with a minimum of physical exertion. He wrote a year later that he was observing instructions and was in the best of health (fig. 3).

Case 5.—In 1922, a boy who had suffered from many acute infectious diseases as a child was brought to the Mayo Clinic on account of poor physical endurance as demonstrated in a swimming test; he had no other symptoms. Because of high systolic blood pressure, he was limited in his activities and given a diet low in protein. He returned on Sept. 1, 1926, for reexamination. Accentuation of the pulmonic second sound and a loud systolic murmur, greatest in the aortic area but also heard to the left of the sternum and in the neck, were observed.

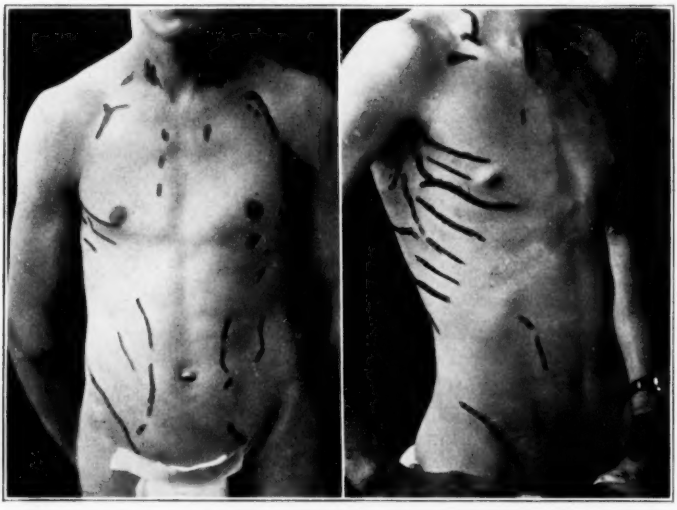

Figure 3 Figure 4

Fig. 3 (case 4).—The muscular development of the subject is well shown. Attention is directed to the superior and inferior epigastric and musculophrenic arteries. In this and the following photographs, the collateral circulation was outlined by palpation on the body of the subject and checked by one or more other physicians.

Fig. 4 (case 5).—Attention is directed to the prominence of the transverse cervical, intercostal, long thoracic, subscapular and circumflex iliac arteries.

The aortic second sound was roughened, but there was no diastolic murmur nor was any precordial thrill palpable. Coarctation of the aorta was first recognized at this time. On April 16, 1927, he was again examined. His mother said that her health had never been better than during the nine months preceding his birth. For about five years, his general health had been good, and he did not have subjective complaints. He was fairly well developed and well nourished, presenting a contrast to the sickly child of 1922, and he was proud of being able to make

his own living. The strictness of the diet had been gradually relaxed, but he was still observing instructions with regard to the avoidance of violent exercise. Dietary restrictions were removed, and three months later his color was better, but he was advised to continue the general regimen as regards exercise (fig. 4).

Comment on Cases 4 and 5.—These two boys, aged 16 years, who were seen within a few days of each other were without symptoms. The first was an athlete of correspondingly good muscular development; the second had been forbidden to take part in athletics and was, therefore, not so strong. The lack of endurance in the latter at the age of 12 was probably more attributable to his various illnesses in the preceding six years than to the congenital lesion of the aorta.

Case 6.—A laborer, aged 46, sought relief at the Mayo Clinic on Dec. 30, 1926, for epigastric distress. He had led an active life, but had never noted dyspnea palpitation, edema, headache, cold feet, nocturia or impairment of libido or potentia. At the time of a former abdominal operation, the surgeon had found the right rectus muscle unusually vascular. A harsh systolic murmur was heard at the aortic area; this was even more pronounced in the back, especially between the vertebral column and the upper part of the left scapula. Since the heart was not enlarged and the blood pressure almost normal, and since the patient was middle-aged and dependent on manual labor for his livelihood and denied cardiac symptoms entirely, it did not seem that an alteration in his mode of life was necessary.

Case 7.—A girl, aged 16, was brought to the Mayo Clinic on March 2, 1925, because of exophthalmic goiter. She had always been annoyed with cold feet, and had had momentary spells of difficulty in walking, but she had never experienced cardiac symptoms until 1922, when nervousness, weakness, palpitation, tachycardia, sweating and intolerance to heat caused her to consult a physician. The basal metabolic rate was found to be + 25, the systolic blood pressure from 160 to 180 and the diastolic from 76 to 80, and a diagnosis of exophthalmic goiter was made; the symptoms subsided spontaneously. Two years later, the thyroid gland had enlarged perceptibly, and during the two months preceding admission to the hospital there had been violent recrudescence of the syndrome of goiter. Vomiting the previous week had been controlled by iodine; some improvement had occurred, but the patient was still critically ill. Stimulation, weakness, stare and sweating were all marked, and there was a loud bruit over each lobe of the thyroid gland. The first sound at the apex of the heart was snapping, and a systolic murmur was heard over the whole precordium, being transmitted to the axilla. The pulse was 110, the basal metabolic rate + 62. After two more weeks of iodine treatment, the enlarged thyroid gland was resected, about one-fourth the normal amount of gland tissue being left on each side. Pathologic examination confirmed the diagnosis of exophthalmic goiter. Immediate convalescence from the operation was uneventful, and there was prompt and striking symptomatic relief with gain in weight.

After dismissal, however, the pulse remained rapid, and when compound solution of iodine was not being taken, the basal metabolic rate varied from + 20 to + 30. The patient returned Aug. 4, 1926. At this time, the left lobe of the thyroid was about twice normal size. During seven weeks of observation the symptoms of exophthalmic goiter could be controlled with iodine, but it became apparent that further resection of the gland would be necessary at some time, and the patient elected to have it done at once. Microscopic examination of the

specimen removed at the second operation was again reported as revealing hypertrophic parenchymatous thyroid gland. Sixteen days later, all evidence of exophthalmic goiter having subsided, the patient was examined again to determine the cause of the high blood pressure (systolic 206, diastolic 90), and coarctation of the aorta was diagnosed. She was dismissed with instructions to take ten drops of a compound solution of iodine daily for ten weeks. She returned on Jan. 3, 1927, for reexamination; at this time, the basal metabolic rate was normal, and she felt well, but there was no change in the vascular condition.

Comment.—The frank exophthalmic goiter masked the presence of coarctation in this case at first. The only other case in which thyroidectomy had been performed in a case diagnosed clinically or at necropsy as coarctation was one,[95] apparently of adenomatous goiter, in which operation was performed more than twenty years before death. Intermittent claudication has been noted in the history in one case previously diagnosed as coarctation of the aorta at the Mayo Clinic and in three so diagnosed elsewhere.

Case 8.—A woman, aged *22*, came to the Mayo Clinic on July 6, 1927, complaining of nervousness and the loss of 10 pounds (4.5 Kg.) in the preceding six months. One sister had always been "nervous," and another had recently become so. Diffuse enlargement of the thyroid had been present for nine years. Three years before coming under observation she had been rejected on applying for work on account of "high blood pressure," and on another occasion on account of rapid pulse. Although strenuous exertion had always caused transient palpitation and tachycardia and she had lost blood through epistaxis many times up to 1925, she had considered herself in good health until the autumn of 1926, a few months after she was married. In September, she was shocked by the death of her father and about the same time she fell down five steps. A few days later, "things got black" before her eyes, she felt dizzy and her heart became rapid for a few minutes. A physician again found her blood pressure high, and prescribed a diet low in protein and salt. Following this, she became nervous and for several weeks apparently was on the borderline of a depressive psychosis. In January, 1927, there was a miscarriage of a six-months' fetus, and the symptoms became worse. The administration of compound solution of iodine (10 drops three times a day) was begun and continued for four months without improvement. The appetite had failed somewhat, and the feet were always cold. The thyroid gland was diffusely enlarged, and a bruit was heard all over it. At the apex of the heart, a systolic murmur was heard which became somewhat louder at the base and was transmitted into the thyroid gland and the infraclavicular fossa. This murmur was also heard distinctly in the left interscapular space. The basal metabolic rate was + *20*, but on further study the diagnosis of coarctation was made; subsequent rates were lower (fig. 5).

Comment.—In the presence of a diffusely enlarged thyroid gland with bruit and thrill, an elevated basal metabolic rate, nervousness, tremor and some loss of weight, the presumable diagnosis would appear to be exophthalmic goiter. However, the patient's admittedly neurotic temperament and the various psychic shocks she had undergone in the previous year may explain some of the symptoms. The failing appetite,

cold feet, absence of exophthalmos and stare, the failure to improve under treatment with iodine and, above all, the general clinical impression, had caused the diagnosis of exophthalmic goiter to be discarded before the explanation of bruits and thrills over the thyroid gland was found in the diagnosis of coarctation.

CASES OF COARCTATION DIAGNOSED AT NECROPSY IN THE MAYO CLINIC

CASE 9.—A male infant was born on Sept. 19, 1924. Respiration was retarded. Two days later, pallor and cyanosis with superficial respiration set in, and the next day he died. The heart was found slightly dilated and weighed 27 Gm. The

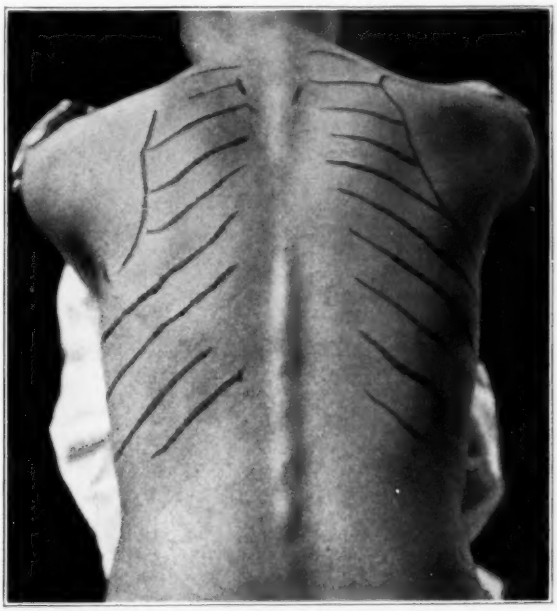

Fig. 5 (case 8).—The anastomosis between the dorsal scapular and intercostal arteries. Blood is evidently flowing toward the aorta in the intercostals.

ductus arteriosus was widely patent, and the lumen of the aorta just proximal to its entrance was somewhat constricted. Other gross anomalies were not present.

CASE 10.—A female infant, aged 3, was brought to the Mayo Clinic on June 2, 1923. She had been delivered with forceps, and artificial respiration had been necessary. She had always been delicate and extremely constipated. Five months previously, she had begun to have fainting spells; in these she would cry out, become pale and fall straight back. There was generalized edema, and the area of cardiac dulness was enormously increased. The action of the heart was regular. There was a definite blowing systolic murmur at the apex and a short blowing diastolic murmur along the sternum. The pulmonic second sound was

accentuated. A diagnosis of congenital cardiac disease was made, and six days later the patient died.

The heart occupied the whole width of the thoracic cavity; it weighed 215 Gm. The right auricle was greatly distended and the right ventricle was 1.2 cm. in thickness as compared with 1 cm. for the left ventricle. There was an interventricular opening 1 cm. in diameter. The ductus arteriosus readily admitted a fine probe. Just proximal to the opening of the ductus into the aorta there was marked constriction of the aorta by a valvelike ring, which, on approximation of the walls, almost closed the lumen. The arch of the aorta proximal to this was slightly narrow as compared with the thoracic aorta. Fetal lobulations of the spleen, incomplete rotation of the intestinal tract, horseshoe kidney, incomplete lobulation of the lung, ascites and anasarca were also noted.

Case 11.—A female infant with gross external anomalies was born on July 11, 1927. She suffered repeated convulsions, the respirations growing rapid and noisy, and died on the fifth day without ever having appeared cyanotic. The cardiovascular system was normal, except for marked constriction of the aorta just proximal to the mouth of the widely patent ductus arteriosus. The additional pathologic diagnosis was, "spina bifida (first four lumbar vertebrae) with meningomyelocele; extreme degree of internal hydrocephalus with hydromyelia; hemorrhages into the brain with terminal meningitis." This case strongly resembles one reported by Dreyfuss.[27]

Case 12.—A man, aged 24, came to the Mayo Clinic on Feb. 16, 1923, complaining of shortness of breath at night and pain in the right side of the neck on exertion. He had enjoyed good health except for occasional occipital headache until his discharge from the United States Navy in 1920. After this he noticed dyspnea with palpitation and tachycardia on mild exertion, and at night palpitation and later orthopnea, which he attributed to the fact that the "weakened artery" on the right side of the neck choked him when he was lying down. In the right supraclavicular fossa there was a tender pulsating mass, giving both systolic bruit and thrill. A diastolic murmur was heard in the aortic area. "Distention of the vessels of the back over both scapulas" was recorded, but pulsation in these vessels, in the abdominal aorta or in the arteries of the lower extremities was not noted. There was no cyanosis or edema. Moderate tenderness over the thoracic vertebrae was observed. A diagnosis of aneurysm of the right subclavian artery was made. Although the circulation in the affected arm was good after operation, the patient died from pneumonia on the tenth day.

The heart was diffusely hypertrophied; it weighed 450 Gm., and the thickness of the left ventricle was 1.5 cm. as compared with 0.4 cm. for the right ventricle. The aortic valve had only two leaflets. The aorta, which showed a minimal amount of arteriosclerosis, was completely obliterated just beyond the origin of the left subclavian at the insertion of a somewhat thickened ligamentum arteriosum. About 2 cm. distal to this, the circumference of the aorta was 3.8 cm. The innominate artery measured 4.5 cm. in circumference, and the branches of the right subclavian were greatly increased in size. From the costocervical trunk arose a tortuous artery 14 mm. in circumference and 7 cm. in length, which passed behind the esophagus to open into the aorta just above the origin of the third intercostal; its lower part was dilated to form an aneurysm about 2 cm. in diameter. The brain and spinal cord were not examined (fig. 6).

Comment.—Although a vestige of the right dorsal aorta is not particularly rare, the presence of such an efficient trunk is exceedingly rare. In this instance it had evidently remained patent because it was needed

as a blood channel; in other words, the obstruction in the left dorsal aorta must have occurred before the atrophy of the right dorsal aorta in the second half of the second month of embryonic life. This anomalous vessel must have been a rather efficient shunt for the aortic current, and perhaps due to it the blood pressure was found normal in the brachial artery; if so, it was of vast clinical significance as it removed a valuable clue to coarctation. In some other cases of bicuspid aortic valve, high pulse pressure has been found and attributed to relative insufficiency of the valve; however, in this and in the four cases of bicuspid aortic valve not associated with coarctation found at necropsy

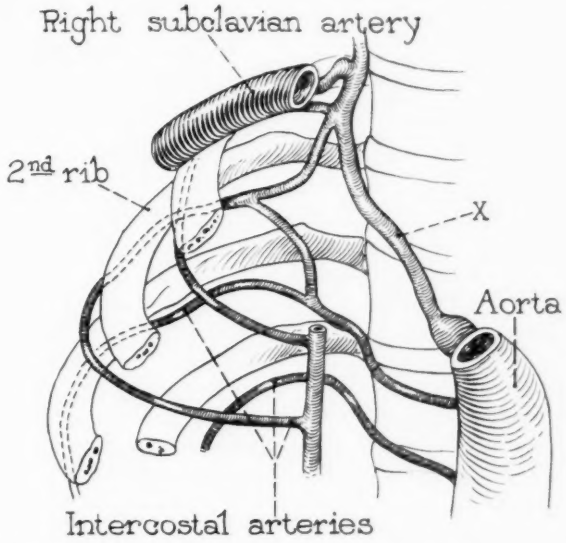

Fig. 6.—Persistent right dorsal aorta (X) in case 12 (diagrammatic).

at the Mayo Clinic, the blood pressure was essentially normal. In the only other case of aneurysm of the right subclavian artery associated with coarctation (clinical diagnosis),[75] death was due to rupture of the aneurysm, and it is probable that in the present case the patient would have died in the same way if operation had not been performed. The presence of a second aneurysm in this case is of interest. In view of the tenderness over the thoracic vertebrae and Haberer's report of the share of the anterior spinal artery in the collateral circulation in his case, it is to be regretted that the cord was not examined at necropsy.

There was nothing of significance in the family history of the adult patients in this series, nor any history of rheumatic fever. The results of the general examination of each patient were essentially negative,

TABLE 2.—*Summary of the Series of Cases in Adults from the Mayo Clinic*

Case	General Health	Size of Heart (Roentgenogram or Necropsy)	Collateral Circulation	Pulsation			Blood Pressure								Electrocardiogram
							Right Brachial		Left Brachial		Right Femoral*		Left Femoral		
				Retinal Arteries	Abdominal Aorta	Femoral Arteries	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	
1	Good	1	Good	Good	None	None	164	86	126	110	90	80	...	..	.....
2	Fair	+	Not found	?	None	None	150	84	...	...	100	..	...	..	Negative
3	Good	Normal	Good	?	None	None	200 158	110 100	180	...	120	..	135	..	Negative
4	Good	Normal	Good	Good	None	None	164	56	102	62	80	60	...	..	Negative
5	Good	Normal	Good	.....	None	None	180 160	100 76	165 156	100 82	108	60	...	..	Negative
6	Good	Normal	Good	Absent	None	None	158	96	154	98	102	80	106	88	Negative
7	Fair	Normal	Good	?	None	None	180 206 176	86 90 104	172	102	90	60	...	..	Negative
8	Fair	Normal	Good	Good	None	None	168	94	164	90	102	88	98	84	Negative
12	Good	2	Present	.....	.....	.....	128	88	122	90	...	..	...	..	.....

* The first definite oscillation of the needle of the Tycos sphygmomanometer (as the obliterating pressure decreased) was taken as the systolic blood pressure in readings on the thigh. In cases 4, 5, 6, 7 and 8, I made all readings except that on the thigh in case 7. In all cases the blood pressure was determined several times, usually by different observers and, except when made at long intervals, and the readings were in close agreement.

except the aneurysm in case 12. The Wassermann reaction of the blood was negative in each case. The retinal arteries were tortuous in the cases examined.

Besides these cases of definite coarctation, four cases of slight constriction of the aorta with slight dilatation proximally were recently observed at the Mayo Clinic. They may be mentioned for two reasons: first, to illustrate varying grades of coarctation as found in the adult, for transition from a slight degree to atresia has previously been traced in infants, and, second, because the slight constriction was proximal to the insertion of the ligamentum arteriosum. It is worthy of note that in two of these cases the heart was distinctly small. But since the cardiovascular system had nothing to do with the previous health or the death of these four patients and the degree of constriction was slight, these cases will not be counted in the statistical study.

COMMENT

Bonnet's general observations have received increasing confirmation. There is no question that his infantile type is a result of prenatal maldevelopment. However, his deduction that the type overwhelmingly predominant in adults is the result of postnatal contraction of Botallian tissue in the wall of the aorta may be challenged. It has been shown that fibers from the ductus arteriosus do not normally extend appreciably into the wall of the aorta, and it has not been demonstrated that they ever do. As Virchow remarked seventy-five years ago, an anatomic hypothesis is a poor basis for a theory. The appearance of scarring and arteriosclerosis so often found near the insertion of the ligamentum arteriosum, both with and without coarctation, has been adequately explained by Meixner. Since the obliteration of the ductus is due to atrophy from lack of function, such a passive process could hardly effect contraction of the aorta, even if its fibers were present in the aorta. Moreover, as Bonnet was puzzled to observe, coarctation has been found associated with a patent ductus; in these cases, certainly this theory is inapplicable. These cases are equally potent arguments against the belief that obliterating endarteritis of the ductus is responsible for coarctation. The chief basis for this idea is the appearance of scarring in this region, which has already been explained.

The improbabilities of these two theories make it necessary only to consider the hypothesis that constriction or obliteration of the aorta at or distal to the mouth of the ductus arteriosus is of developmental origin. Congdon has shown that the segment of the definitive aorta represented by the left fourth branchial arch may be distal to the mouth of the ductus. If one continues to accept the older view in some cases, the site of coarctation is that segment of the aorta represented by the fourth arch

in all cases. This arch when proximal to the ductus undoubtedly may become occluded or fail to develop normally from some inherent defect or other cause; it is then reasonable to assume that this embryonic structure when distal to the ductus may also be subject to maldevelopment. If this occurs in utero, the collateral circulation may be mapped out and developed at the same period and in the same way as other definitive arteries, and thus cause little disturbance. Since no additional strain would be placed on the right ventricle under such circumstances, it is not surprising that the interventricular septum should develop normally, as it usually does in the adult type.

Of the positive arguments that coarctation of this type is the result of defective arterial primordia, one of the most important is the common association of other developmental defects of the vascular system. Rupture of the aorta without aneurysm and aneurysm of the aorta or of cerebral or other arteries in nonsyphilitic young persons so often associated with coarctation are probably a result of imperfect development. Bicuspid aortic valve, one of the rare anomalies, is found in about 25 per cent of the cases in adults, and general hypoplasia of the aorta, which seems to be half as common as coarctation, is associated in about 10 per cent. Other examples of serious maldevelopment are not infrequent. Thus the presence of associated arterial or valvular anomalies is additional support for the embryonic origin of coarctation in the adult. Further, the case from the Mayo Clinic and the several reviewed in the literature in which the constriction was proximal to or involved the origin of the left subclavian and, above all, the new case which I have reported in which the right dorsal aorta was persistent, must all have dated from the second month of embryonic life.

In the series of fifty-seven cases in adults which I have reviewed definite syphilitic changes in the aorta were found in only two; in a number it is expressly stated that there was no evidence of syphilis. These figures are in accord with those of earlier authors. As evidence of the disease is infrequent in such cases, and since there is little to show that syphilis can obliterate a large artery, the burden of proof that syphilis is of etiologic significance in coarctation rests on supporters of the theory that it is.

However, if the challenge to Bonnet's division with regard to pathogenesis is made good, this classification remains of clinical value as of the 323 cases of coarctation verified at necropsy, death occurred during the first year in 125 and during the first decade in 142. Of the 173 persons who survived this period and whose ages are given, 112 died between the ages of 16 and 40 inclusive; forty-six of these, in the third decade.

In three cases, collateral vessels were looked for but not found during life; the diagnosis in such cases would be strongly suggested by the marked difference in blood pressure in the brachial and femoral arteries. The clinical reports of cases studied that came to necropsy mentioned the presence of collateral vessels twenty-eight times; in these, atresia was found twelve times and extreme stenosis, sixteen; of the eighteen definitely diagnosed in life, atresia was present in eight cases and extreme stenosis in ten. Postmortem protocols show that collateral arteries were often overlooked in life; indeed one case[24] was diagnosed by the pathologist from external examination. The detection of pulsating vessels along the vertebral border of the scapulas and elsewhere over the thorax is therefore presumptive evidence of marked narrowing or occlusion of the aorta at the beginning of the descending part, although extreme stenosis can be distinguished from atresia only at necropsy. Visible pulsation of the arteries of the neck, a prolonged systolic murmur in the interscapular space or high pulse pressure should suggest a search for these. Systolic blood pressure exceeding 150 was found in thirty-three of thirty-five cases in which the systolic pressure was given and a pulse pressure exceeding 70 in twenty-two of twenty-seven cases in which it was given. This high pulse pressure, together with the bruit and thrill over the thyroid gland, emphasize, as Loriga pointed out forty years ago, that these data are insufficient for the diagnosis of exophthalmic goiter, which they are likely to suggest. Collateral circulation due to intrathoracic tumor is so rare that it can seldom confuse the picture. A total of eight cases has been reported in which no evidence of collateral circulation was found at necropsy.

In some cases, such as Horder's, coarctation is not intrinsically the most important factor in the death of the patient. In this instance, the constriction was mild, and the rupture of the aorta was evidently due to defective development at the site of the rupture and was not secondary to the coarctation. At least thirty-five cases already referred to belong in this group. There is another group in which the narrowing of the trunk is not marked and is of merely pathologic interest. The majority of such cases cannot be diagnosed clinically, and it is not important that they should be.

The circulation to the lower part of the body is sometimes functionally perfect in cases of extreme coarctation, as proved by the women who have borne several children, and it may be only an incidental postmortem observation, as is proved by the men who have led strenuous lives as soldiers, sailors or laborers. However, it is the duty of the physician to recognize, whenever possible, coarctation without symptoms, for after symptoms of cardiac failure appear it is too late to advise the patient that he may have a better chance of avoiding cardiac failure or

rupture of a vital vessel. These are real dangers in cases of coarctation; for 147 persons with coarctation, verified at necropsy in a series of 196 adults, died from causes more or less directly related to the stenosis. Sixty-eight died from gradual cardiac failure; sixteen died suddenly from the same cause. Spontaneous rupture of the aorta caused the death of thirty-eight persons, and cerebral hemorrhage of twenty-five more. It has been appreciated for some time that there is a peculiar relationship between congenital cardiac disease and subacute bacterial endocarditis; in six of the sixty cases in adults reviewed or reported in this paper, death occurred in this way, as well as in a number in the earlier reviews. Endocarditis was present in another instance in this series, and bacterial aortitis was the cause of death through rupture of the aorta in two other cases.

As 76 of the 180 subjects aged more than 5 years, whose age is available, died during the years between 16 and 30 inclusive, and since 36 others died during the next decade, the responsibility of the physician who is consulted by a young person with this anomaly is great. When of clinical significance, coarctation can usually, if not always be diagnosed. The possibility of detecting it should cause the physician who makes routine examinations of large numbers of young persons to bear it ever in mind. It may be emphasized again that many of the victims of this condition were young athletes who died during or shortly after exercise, and who might have achieved their normal life expectancy if all unusual strain on the cardiovascular system had been removed. The possibility of the presence of coarctation is an additional reason for the general examination of every one contemplating violent physical exercise, irrespective of his previous health.

When the diagnosis is made, not only should a regimen of limited physical activity be prescribed, but all possible foci of infection should be removed on account of the danger of bacterial endocarditis or aortitis. There is no apparent indication for dietary restriction.

SUMMARY

Narrowing or obliteration of the aorta in the region of the mouth of the ductus arteriosus or its vestige is believed to be due to absence, atrophy or imperfect development of the left fourth branchial arch. Syphilis is not an etiologic factor.

The division into the infantile type, in which the constriction is proximal to the ductus, and the adult type, in which it is at or just distal to it, though not precise, is convenient morphologically and clinically.

Coarctation has been found in 127 necropsies on infants and young children. The clinical diagnosis in such cases is of little or no actual

importance, because coarctation of the infantile type is rapidly fatal, or, if of the adult type, hardly a factor in causing death.

Coarctation has been found in at least 196 necropsies on older persons. More than 40 per cent of these were from 16 to 30 years of age, and more than 70 per cent died from cardiovascular causes. In addition, coarctation in thirty-five cases was overshadowed by other cardiovascular defects of developmental origin.

Coarctation has been diagnosed clinically in seventy-eight cases and corroborated at necropsy in twenty-one of these. The diagnosis is often suggested by an unusually high pulse pressure or by a loud systolic murmur in the left interscapular space, and confirmed by the presence of pulsating superficial arteries over the thorax and the diminution or absence of pulsation in the abdominal aorta and femoral arteries.

Coarctation once diagnosed indicates the removal of possible foci of infection and, especially if the patient is a robust, athletic young man, a regimen of limited physical activity.

CHONDROMA OF THE SPINE ASSOCIATED WITH A TRANSVERSE MYELITIS

JOSEPH FELSEN, M.D.
NEW YORK

Cartilaginous tumors are frequently encountered as small outgrowths from preexisting cartilaginous structures (ecchondroses) and as larger growths originating in cartilage or other tissues (enchondromas). Usually the larger neoplasms are readily diagnosed because of the tendency to cause visible deformity or symptoms of obstruction. Of all the bony structures the spine is singularly free from obstructive tumors of this type. It is because of the rare occurrence of this condition and the unusual pathologic aspects that the following case is reported.

REPORT OF A CASE

Clinical History.—A negro, a laborer, aged 23, in September, 1918, was confined to the hospital for two weeks with an attack of influenza. In December, 1918, he complained of frequent "drawing and sharp, shooting" pains in the lower part of the abdomen and both lower extremities, accompanied and followed by marked weakness of the legs.

In January, 1919, he suffered an attack of mumps, after which weakness of the legs became more pronounced. He experienced sharp pains in the lower part of the back. Within a period of seven days, he gradually lost power of voluntary movement in both lower extremities. In the following eleven months, he received intravenous treatment for syphilis (details not available), without improvement.

In July, 1920, he entered the U. S. Public Health Service Hospital, Cape May, N. J. Clinical notes at this institution indicated the presence of a paraplegia, urinary and fecal incontinence, nocturia, pain in the lower spinal region and impaired sensation over both lower extremities.

In September, 1920, he was admitted to the U. S. Public Health Service Hospital 38, New York. The following is a report of a physical examination made at that time.

Physical Examination.—A young negro was lying quietly in bed. The knees were semiflexed and the feet extended. Occasional jerking movements of the lower extremities were noted. Decubitus ulcers, approximately 3 by 5 cm. and 2 by 4 cm. were seen over both buttocks, exposing the muscle tissue. There was no evident enlargement of the heart. A presystolic murmur was present and confined to the apical region. In the upper thoracic region of the spine, there was a slight dorsal irregularity of contour, which was markedly tender to pressure. The cervical, axillary and inguinal nodes were palpable.

There was a temporal pallor of the right optic disk. The pupils were irregular, unequal (the left being miotic) and sluggish in reaction to light. Flaccid paraplegia involved the muscles of the lower part of the trunk, causing difficulty in maintaining an upright posture even while sitting. There were clonic tremors of the legs, particularly of the left one, caused by any attempt at voluntary movement of the upper part of the body or passive motion of the leg or foot. These movements

ceased on deep pressure. The muscles of the legs were flabby. The faradic response of the muscles of the right leg and of the thigh were 0.1 microfarad; left leg, 0.05 microfarad and left thigh, 0.01 microfarad.

Below a level corresponding with the third rib, tactile pain and thermic sensation were abolished. In this area, the patient could not discriminate between two points, and the posture sense of the legs was lost. The vibratory sense tested by means of the tuning fork was interpreted as pain. Just above this analgesic and anesthetic area was a zone of hyperesthesia and hyperalgesia.

All reflexes were abolished in both lower extremities. There was no Babinski sign or true ankle clonus. The cremasteric and abodminal reflexes were absent. Involuntary micturition and defecation were present.

Laboratory Data.—The Wassermann reaction was negative on five occasions. One blood culture was negative a few days before death, having been taken during a septic period. Three examinations of the spinal fluid were made. The following report is representative: amount, approximately 25 cc.; color, xanthochromic; turbidity, none; cytologic, 40 lymphocytes per cubic millimeter; globulin, present;

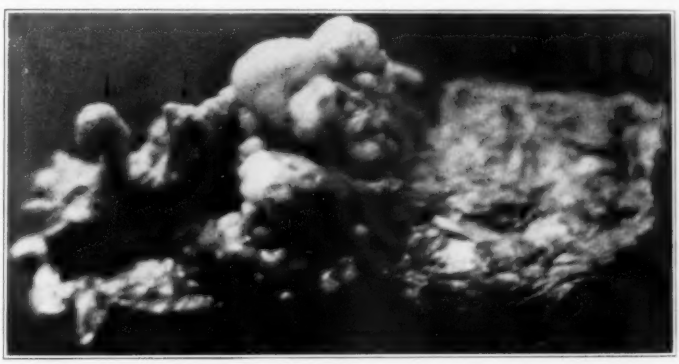

Fig. 1.—Lateral view (left side) of spinal column showing posterior nerve root and sympathetic trunk emerging from tumor mass.

sugar, none; collidal gold test, invalidated by the presence of dissolved hemoglobin; Wassermann reaction, negative on three occasions, and guinea-pig inoculation, negative for tuberculosis at the end of six weeks.

Roentgenographic Studies.—Roentgenographic studies of the chest revealed a mass, somewhat triangular in outline, approximately 5 cm. in length and 3 cm. in width, occupying the region of the second rib on the left side. The mass extended to the median line and invaded the bodies of the first and second dorsal vertebrae. Examination of the upper dorsal to the lower sacral spine by means of the Dandy technic revealed an ovoid, irregularly outlined mass extending from the articulation of the third left rib, close to the vertebral junction, obliterating these structures. The mass was distinctly calcareous and probably not malignant.

Clinical Course.—The clinical course was marked by a gradual development of sepsis due to the progressive extension of decubitus ulcers on the buttocks. Death occurred on Oct. 15, 1920, approximately two years after onset of the symptoms.

Gross Pathology.—The specimen submitted for examination consisted of a resected portion of the spinal column, including the spinous processes and bodies of the last two cervical and upper three dorsal vertebrae with about 5 cm. of rib attached to three of the latter. Extending anteriorly and to the left, involving the spinous processes and posterior aspect of the bodies of the first and second dorsal vertebrae and adjacent portions of the ribs on the left side was a hard, grayish, partly translucent, smooth, irregularly lobulated tumor. The lobules varied in size from 2 to 25 mm. A posterior nerve root and what was apparently a trunk of the sympathetic nerve were seen to emerge, somewhat distorted, between and firmly embedded in lobules of the tumor. On removing the laminae of the involved and adjacent vertebrae, the mass was seen to project directly forward into the spinal canal for a distance of from 15 to 17 mm. over a vertical extent of 40 mm. The posterior nerve roots were stretched taut, and the cord itself, covered by its membranes, was compressed to a mere ribbon. A small amount of old clotted blood was seen in two small triangular spaces just above and below that portion of the tumor which projects into the canal. Many small varicosities were to be seen on the posterior surface of the vertebral bodies for

Fig. 2.—Lateral view (right side) of spinal column, with laminae removed, showing the tumor projecting forward into the spinal canal and compressing the cord. (Arrows point to cord.)

a short distance above and below this region. Some calcified portions and small round areas of cystic degeneration were evident in the larger lobules. Typical golden yellow spinal fluid was present in the canal below the tumor mass. By careful dissection, a perichondrium could be demonstrated encapsulating the tumor, and septums of connective tissue separated the lobules. The cut section was typically bluish and translucent.

Microscopic Pathology.—Sections taken from one of the larger lobules showed a mixed hyaline and fibrocartilaginous structure. The cells appeared to be more numerous than in normal cartilage. They occurred singly or in groups of from two to six lying in clear elongated cell spaces. They appeared to be almost round, except where many were grouped together, in which case the opposing surfaces were flattened. Variations in size, irregularity and distribution and arrangement indicate an abnormal cartilaginous structure. Thin sections do not take a deep stain with hematoxylin-eosin.

EPICRISIS

Clinical Aspects.—The etiology of chondroma is not always clear. The majority of these tumors occur early in life, about the time of puberty. Most chondromas occurring in connection with bone begin before ossification of the epiphysis has occurred, at a period in which the bone is actively growing and vascular. Multiple chondromas of the spine are hereditary and congenital. The hereditary predisposition is

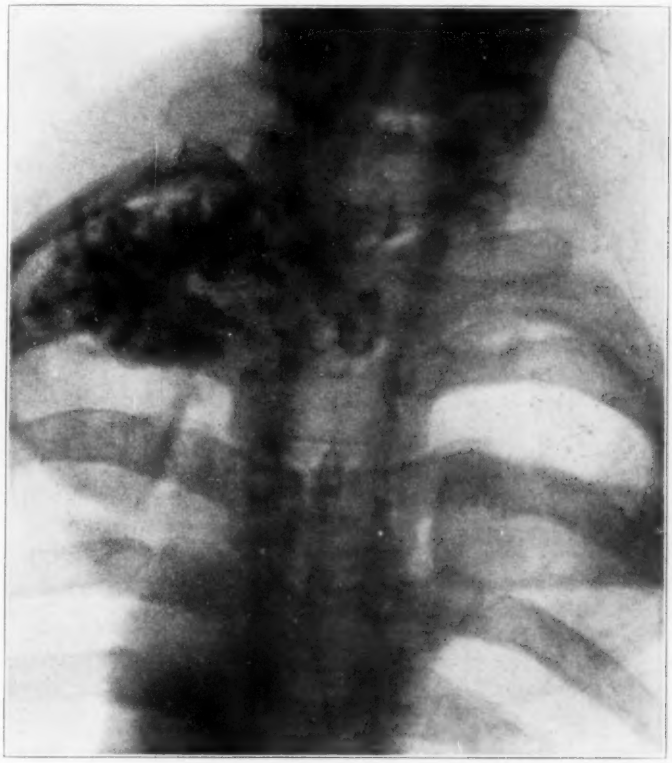

Fig. 3.—Roentgenographic appearance of tumor mass (anteroposterior view). Note the diffuse distribution of calcareous deposits. Positive print.

stressed by Weber,[1] who observed this type of tumor in several members and three generations of the same family. Herxheimer [2] attributed

1. Weber, C. O.: Die Knochengeschwülste, Amtl. Ber. ü. d. Versamml. deutsch. Naturf. u. Aerzte, Göttingen **31**:164, 1860.

2. Herxheimer, G.: Grundlagen der pathologischen Anatomie, ed. 2 and 3, p. 102.

many of these chondromas to heterotopic rests, while Virchow [3] pointed out that the frequent occurrence of chondroma in young people is caused by displaced cartilaginous islands cut off during endochondral ossification. Borst [4] described isolated islands of cartilage in rachitic bone, and Müller [5] found similar deposits in the periosteum of the ribs. The theory of heterotopic rests is probably not applicable to all chondromas, as periosteum and endosteum normally form cartilage readily. Trauma and inflammation are factors in some cases. In this

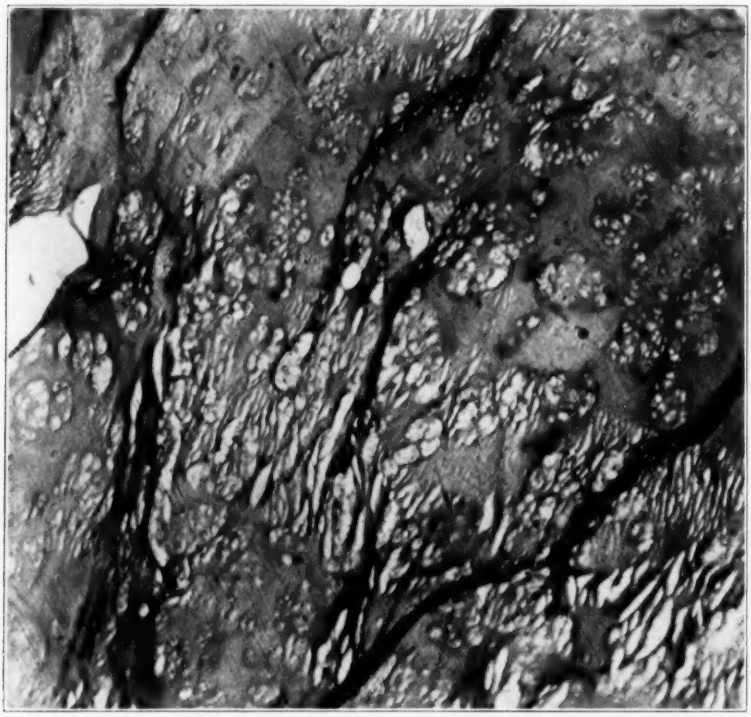

Fig. 4.—A section taken from the tumor. Note the variation in the size and shape of the cells as well as their irregular distribution and arrangement.

patient the onset of symptoms following influenza and mumps appeared to be significant. A possible infection of the intervertebral disks followed by marked overproduction of cartilage—a process so common in the negro—might account for the formation of a chondroma.

3. Virchow, R.: Deutsche Klin. **9**:90, 1864.
4. Borst, M.: Pathologische Histologie **2**:342, 1926.
5. Müller, E.: Beitr. z. path. Anat. u. z. allg. Pathol., vol. 57, pp. 232-281.

Transverse lesions of the spinal cord as a result of caries or tumor of the spine are rarely complete. In total transverse lesions, there is complete sensory and motor paralysis and complete loss of tendon reflexes in parts supplied below the segmental level of the injury. The muscular paralysis is of the flaccid type, with rapid wasting and loss of faradic excitability. The development of paraplegia is gradual and usually precedes the loss of sensation. The early symptoms are weakness of the lower limbs or peculiar sensations of numbness, tingling or pins and needles. It is interesting to note that paraplegia caused by pressure on the spinal cord may persist for as long as a year and yet recovery be complete after removal of the tumor. The zone of hyperesthesia described in this case is not always present. There is loss of sphincteric control (bladder and rectum). Certain skin reflexes may occasionally persist (e. g., plantar reflex with dorsal flexion of the great toe).

Physiologic Aspects.[6]—Based on present knowledge of the functions of the tracts, the location and extent of neuro-anatomic injury in the case presented may be stated briefly as follows: (1) Sensory pathways: funiculus gracilis, cuneatus, cerebellospinalis, anterolateralis superficialis, cerebrospinalis lateralis, lateralis proprius, which constitute long ascending tracts in the posterior and lateral funiculi of the cord. Their function is to convey muscle sense. Short association tracts of the lateral and anterior funiculi, which are probably the pathways for touch, pain and temperature. (2) Motor pathways: funiculus cerebrospinalis lateralis et anterior, intermediolateralis, which control voluntary movement. (3) Reflex pathways. In this connection, mention may be made of the physiologic centers for defecation and bladder control. These probably lie in the lumbar cord, both acts being in the nature of involuntary reflexes.

In explanation of the length of time the patient survived an almost total deprivation of most of the spinal cord, it is interesting to recall the experiments of Goltz and Ewald.[7] In steps, they removed the entire cord except the cervical and a small part of the upper thoracic regions, thus simulating the lesion in my patient. With great after-care, they succeeded in keeping their animals alive for a long period, the digestive circulatory and excretory organs performing in a normal manner. This indicates that the visceral organs are more independent of direct control by the nervous system. The adaptability of the cordless portion of the animal and the power to preserve a constant body temperature were less than normal and the susceptibility to inflammatory disturbance greatly increased. The gradual loss of functioning cord tissues by

6. Howell, W. H.: Text Book of Physiology, Philadelphia, W. B. Saunders Company, 1911, 155-156, 168-182, 244-250, 722-723 and 843-844.

7. Goltz and Ewald: Arch. f. d. ges. Physiol. **63**:362, 1896.

pressure of the tumor probably afforded an opportunity for the patient, as in the case of Goltz' animals, to adapt himself to a modified mechanism of nervous control. Clinical reports indicate recovery of function after removal of tumors which have compressed the spinal cord for as long as a year.

Histologic Aspects.[8]—Cartilage is a tissue of mesodermal origin. The cartilage cell seems to be an end-product of the connective tissue cell which has acquired the special function of producing fibroglia, collagen or elastic fibrils and the ability to secrete a dense homogeneous intercellular substance known as chondromucin.[9] In the process of transformation, the fibroblast becomes spherical or flattened and appears to lose its fibroglia fibrils. At first the cartilage is wholly cellular. As the intercellular substance increases, lighter and denser areas are formed about individual cells or groups of cells giving the appearance of hyaline capsules. Hyaline, fibrous or elastic cartilage results depending on the nature and quantity of the intercellular matrix. New cartilage[10] is always the product of cells at the periphery which are more like fibroblasts in appearance. The latter cells form a fibrillar connective covering, the perichondrium, which blends almost imperceptibly with the superficial layers of cartilage. In a similar manner, cartilage cells may arise from fibroblasts composing periosteum. The cartilage cell possesses ameboid properties and is prone to metaplastic change.[11]

Pathologic Aspects.—Cartilaginous growths occurring as simple hyperplasias of preexisting cartilage are usually multiple and small, springing from the edges of the articular cartilage and passing through the capsular ligament. This type of hyperplasia is generally referred to as an ecchondrosis and is probably the result of chronic irritation. The ribs, larynx, intervertebral disks and the area about joints are rather common sites. The general structure is that of normal hyaline or fibrocartilage, being surrounded by a normal perichondrium which, according to von Rindfleisch,[12] is the point of origin.

True progressive neoplasms composed of cartilage occur in the same regions as ecchondroses, but also in soft tissues and internal organs. This type of tumor is known as chondroma or enchondroma and is

8. Bailey, F. R.: Text Book of Histology, New York, William Wood & Company, 1910, p. 90.

9. Mallory, F. B.: The Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1923, p. 291.

10. McFarland, J.: Surgical Pathology, Philadelphia, P. Blakiston's Son & Company, 1924, p. 243.

11. MacCallum, W. B.: Text Book of Pathology, Philadelphia, W. B. Saunders Company, 1924, p. 950.

12. Rindfleisch, E.: Lehrbuch der pathologische Gewebelehre, Leipzig, 1886, p. 155.

often probably the sequel of a simple hyperplasia. It is found most frequently on the metacarpal bones and phalanges, usually being multiple and at the epiphyseal line. The femur, ribs, scapulae and pelvis are not infrequent sites. The typical chondroma is usually seen as a dense, rounded, nodular or lobulated tumor, appearing translucent, pale bluish or opalescent white on section. The gross appearance depends largely on the age, rapidity of growth, state of nutrition and type of cartilage making up the tumor. The size may vary from a single small tumor weighing a few grams to a large lobulated mass of several kilograms (pelvis). There is an encapsulating dense layer of connective tissue made up partly of perichondrium, which is the source of growth and partly of displaced and compressed connective tissue derived from the invaded area. The lobulation is outlined by fibrous vascularized septums which spring from the capsule and, according to Ewing, represent growths from multiple centers. Nutrition is maintained by a system of lymph spaces from the periphery of the lobule (von Rindfleisch and Borst [13]). Chondromas are usually broadly connected with bone or cartilage. They may be partly embedded in the marrow cavity, the superficial portion breaking through the cortex. The external or periosteal chondroma may, by pressure atrophy, cause the formation of a fossa in the surface of the bone. The centrally situated chondromas are usually multiple. Some cases have been reported in which nearly every bone was involved.

Secondary changes are common. Calcification or ossification, mucinous degeneration with cyst formation, are the usual changes encountered. The tendency to calcification or ossification appears to be enhanced by the presence of many vascularized septums of the connective tissue. Virchow [14] and von Recklinghausen [15] believe that the highly vascularized areas found about many chondromas play an important part in the development of the tumor. Blood vessels may grow into the cartilage as in normal endochondral ossification and convert it into bone. Ossification is most common in tumors springing from the junction of epiphysis and shaft of a long bone. Cysts filled with mucinous, serous or fatty material may be formed. Large tumors which reach the skin may stretch it and cause ulceration. Most chondromas occurring in connection with bone begin before ossification

13. Von Rindfleisch and Borst, in Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1922, pp. 185 and 189. Delafield, F., and Prudden, T. M.: Text Book of Pathology, New York, William Wood & Company, 1925, p. 402.

14. Virchow, R.: Cellular Pathology, trans. by Chance, New York, R. M. De Witt, 1860, p. 445.

15. Von Recklinghausen: Multiple Enchondrom der Knochen in Verbindung mit multiplen phlebogenen cavernösen Angiomen der bedeckenden Weichtheile, Virchows Arch. f. path. Anat. **118**:4, 1889.

of the epiphysis has occurred, at a period when the bone is actively growing and vascular.

The microscopic processes in chondroma are largely the same as those seen in the structure of normal cartilage. Ernst [16] described all of the variations in great detail. Any or all three types of cartilage may be found in one tumor, but hyaline cartilage is most frequently seen. Ranvier [17] divided chondromas into four groups: (1) single lobe of hyaline cartilage; (2) several lobules of hyaline separated by fibrocartilage; (3) fetal cartilage, and (4) cartilage with stellate cells. The general appearance of the cells resembles that of normal cartilage, except that they vary greatly in size and shape and in the orderly grouping of cells lying in lacunae with opposed surfaces flattened. The cells may contain vacuoles ("physaliden" of Virchow), mucin or calcium granules. Glycogen and fat granules are commonly present. The size and shape may vary from large polymorphous cells to stellate rounded or small spindle-shaped forms, the latter lying near the periphery and constituting the actively growing portion of the tumor. This region adjoins the vascularized stroma which, by means of its septums separates and brings nutriment to the individual lobules. As growth proceeds, this stroma is stretched, and the cells farthest removed from it are apt to undergo mucoid degeneration, calcification or necrosis.

The matrix of a chondroma is usually hyaline, but may be fibrous or elastic. Calcium deposits first affect the matrix and appear as deeply basic staining granules made up of phosphate and carbonate. Ribbert is of the opinion that the matrix is a product deposited under cellular influence. The younger portion of the tumor is apt to be more cellular and contain less matrix. The cells may or may not possess a capsule.[18] According to Aschoff,[19] the young cells generally are devoid of a capsule. When present, the capsule shows a fibrillated structure.

SUMMARY

A case of chondroma of the spine associated with transverse myelitis is described. The slow development and benign character of the tumor suggest that even delayed surgical measures may be consistent with cure. Persistent arsenical treatment of a negro with symptoms pointing to a lesion of the spinal cord should be avoided without preliminary roentgenographic studies of the spine.

667 Madison Avenue.

16. Ernst, P.: Ueber den feineren Bau der Knorpelgeschwulste, Beitr. z. Path. Anat. **38**:67, 1905.

17. Ranvier: Contribution à l'étude de la structure et du développement des tumeurs cartilageneuses, Bull. de la Soc. Anat. de Paris **40**:534, 1865.

18. Zeigler, E.: General Pathology, trans. by Symmers, New York, William Wood & Company, 1921, p. 298.

19. Aschoff, L.: Pathologische Anatomie, Jena, G. Fischer, 1913, p. 690.

THE RECIPROCAL RHYTHM

REPORT OF A CASE IN WHICH AURICULAR TACHYCARDIA WITH PARTIAL A-V DISSOCIATION AND ATRIOVENTRICULAR BRADYCARDIA, WITH RECIPROCATING RHYTHM, WERE PRESENT *

WILLIAM DOCK, M.D.
STANFORD UNIVERSITY, CALIF.

In 1913, Mines [1] described a curious rhythm occurring in the heart of the ray and of the frog after electrical stimulation. This rhythm continued for a considerable period after a single shock, and could be interrupted and abolished by a second stimulus applied either to auricle or ventricle. The mechanism consisted of a sequence of auricular and ventricular contractions, equally spaced and apparently due to an impulse originating in either chamber and transmitted over the usual conduction path to the other, returning again to the first over the same pathway and repeating this process indefinitely. Mines assumed that part of the conduction pathway must have been refractory during the passage of the impulse in one direction, with recovery and transmission in the opposite direction when the second chamber contracted and while the initially active fibers were refractory.

A similar mechanism has not been observed in the heart of mammalia, either experimentally or accidentally. However, in 1924, Drury [2] recognized the similarity between the "reciprocating rhythm" of Mines and a type of bigeminy which occurs during atrioventricular rhythm in man. In this condition an auricular beat falls near the end of systole of the first ventricular beat of the couplet.

This arrhythmia was first described by Wenckebach [3] in 1906, from polygrams taken of a boy, aged 12 years, with compensated rheumatic heart disease. He interpreted these curves as showing dissociation of the auricles, the left auricle maintaining a steady rhythm in the ventricles, the right auricle beating more slowly. When the right auricle contracted after the refractory period of the ventricles had ended, they responded to it, giving the appearance of an interpolated extrasystole in the tracing

* From the Department of Medicine, Stanford University School of Medicine.

1. Mines, G. R.: On Dynamic Equilibrium in the Heart: Reciprocating Rhythm, J. Physiol. **46**:376, 1913.

2. Drury, A. N.: Paroxysmal Tachycardia of A-V Nodal Origin, Exhibiting Retrograde Heart-Block and Reciprocal Rhythm, Heart **9**:405, 1924.

3. Wenckebach, K. F.: Beitrage zur Kenntnis der menschlichen Herztätigkeit. Ueber Dissoziation der Tätigkeit beider Vorkammern, Arch. f. Anat. u. Physiol., Physiol Abteil., p. 349 and Taf. IV, p. 561, 1906.

of the radial pulse. As polygraphic curves illustrative of this disorder are rare, I have reproduced one of Wenckebach's curves (fig. 1).

The electrocardiogram of this type of bigeminy was described by Gallavardin [4] in 1914, in two patients who had nodal rhythm as a result of the administration of atropine or of ocular pressure. Gallavardin regarded the auricular and ventricular complex which composed the second half of the couple as a normal supraventricular beat. White,[5] who reported a similar case in 1915, described the second ventricular beat as due to a return to the ventricle of the impulse which had reached the auricle by retrograde conduction. He reported three later cases,[6] Gallavardin reported another,[7] and Wilson [8] observed the same phenomenon in a patient in whom nodal rhythm was a result of atropine medication. Wilson explained the coupling as due to ventricular response to an auricular beat falling between the R and T wave. Bishop [9] reported a

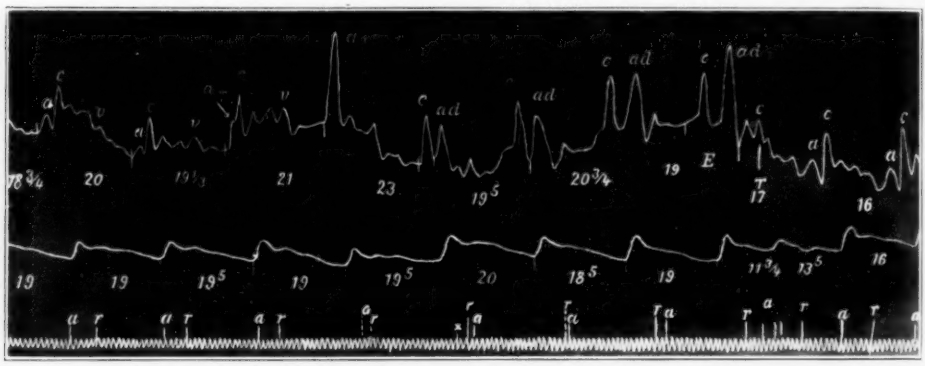

Fig. 1.—Polygram published in 1906 by Wenckebach showing nodal rhythm, with progressive lengthening of interval between ventricular (*c*) and auricular (*a*) waves. At *E* the auricular wave comes after the refractory period of the ventricle and a reciprocal beat (*c* and on the radial pulse curve) follows.

---

4. Gallavardin, L.; Dufourt, P., and Petzetakis: Automatisme ventriculaire intermittent, Arch. mal. du coeur. **7**:1 (Jan.) 1914.

5. White, P. D.: A Study of Atrioventricular Rhythm Following Auricular Flutter, Arch. Int. Med. **16**:517 (Oct.) 1915.

6. White, P. D.: The Bigeminal Pulse in Atrioventricular Rhythm, Arch. Int. Med. **28**:213 (Aug.) 1921. Jones, T. D., and White, P. D.: Atrioventricular Nodal Rhythm, Am. Heart J. **2**:266 (Feb.) 1927.

7. Gallavardin, L., and Gravier, L.: Bradycardie nodale permanente, Arch. d. mal. du coeur. **14**:71, 1921.

8. Wilson, F. N.: The Production of Atrioventricular Rhythm in Man After the Administration of Atropine, Arch. Int. Med. **16**:989 (Dec.) 1915.

9. Bishop, L. F.: Specific Action of Atropine in Relieving Certain Irregularities of the Heart Beat, J. A. M. A. **77**:33 (July 2) 1921.

case of nodal rhythm in which bigeminy occurred as a result of atropine medication. He, like Gallavardin, regarded the couple as due to a normal beat interpolated in an atrioventricular rhythm. Peters [10] considered the second beat as a "sinus extrasystole." The reciprocal rhythm, so named by Drury, differs from the reciprocating rhythm of Mines in that the mechanism is not constant but consists of a single ventricular response to an auricular beat arising from the atrioventricular node and occurring late in relation to the ventricular beat which originated simultaneously. In both reciprocal and reciprocating rhythm, partial conduction in both directions is postulated to account for the return of an impulse over a pathway which it has just traversed. Part of the conductions system must be refractory during conduction in one direction, and part during conduction in the opposite direction.

White found that atropine increased the rate of the atrioventricular rhythm without affecting the coupling, the fast rate leading to a prolonged R-P interval. This is confirmed by the action of atropine in Bishop's case and in our own. In one case,[7] the coupling resulted from a prolonged R-P interval due to vagal stimulation. In our case vagal pressure diminished the tendency to coupling. The disturbance of vagal and sympathetic tone necessary for the occurrence of atrioventricular rhythm seems to vary from case to case. Although vagal release seems to be the most constant cause, increased vagal tone (by digitalis or ocular pressure) is at times an effective agent. It seems reasonable to believe that the same factors which cause nodal rhythm will lead to reciprocal rhythm if they act more intensely, for the greater the atrioventricular rate and the degree of retrograde block, the more often will reciprocal beats occur.

In the case to be described, the sequence of events is of interest. Auricular tachycardia was present for twenty-two days, then nodal and reciprocal rhythm appeared when the patient was fully digitalized and gradually reverted in four days to sinus rhythm. Eight days later, there was a recurrence of persistent nodal and reciprocal rhythm. The variation in degree of bundle branch block in the reciprocal beat is also noteworthy. Its occurrence in couples of shorter duration and its absence in those which are longer is significant of the critical state of the entire conduction system during reciprocal rhythm.

REPORT OF CASE

The electrocardiographic records to be described were obtained during a severe break in compensation of a women, aged 38, who for ten years had had evidence of heart disease due to mitral stenosis. Although ascites, hepatic enlargement and cyanosis were marked, orthopnea was notably absent at all

10. Peters, J. T.: Beitrag zur Kenntnis der irregulären Bradycardien beim Menschen, Wien. klin. Wchnschr. **36**:1307, 1924.

times. Palpitation on effort had been present for some time, but a persistent tachycardia during rest and activity first occurred six days before these observations began. Two days before the first records were taken, she had a regular thready pulse, 170 per minute, but on rest in bed a regular rate of 80, occasionally falling to 40 or 60 and then becoming somewhat irregular, was observed. The jugular veins were distended; the jugular pulse was 160 or more. The clinical diagnosis was auricular flutter, mitral stenosis and myocardial insufficiency.

Auricular Tachycardia or Flutter; Partial Heart Block.—Electrocardiographic records taken on September 10, 14, 19, 20 and 21 (fig. 2) all gave evidence of an abnormal auricular mechanism, with diphasic P waves recurring regularly. The auricular rate over these twelve days varied only between 180 and 186. The ventricular complexes occurred irregularly at all times except on September 19, when the ventricular rate was 90 and the auricular, 180. In all other tracings ventricular responses occurred in response to every second to fourth auricular beat. While it is well recognized that slow auricular flutter may give auricular complexes simulating the normal, it seems more logical when evidence of con-

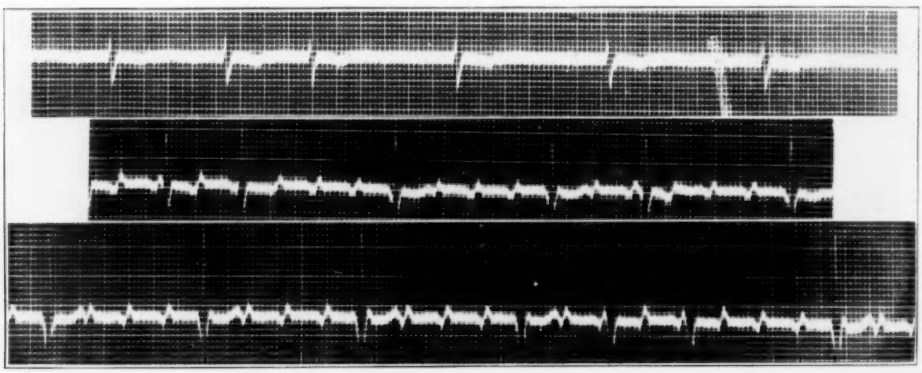

Fig. 2.—Leads I, II and III of electrocardiogram made on September 10, showing auricular tachycardia, partial heart-block, 4:1, 3:1 and 2:1 rhythm. Auricular rate 186 per minute.

tinuous auricular electrical activity does not occur in any of the leads to consider the disturbance as due to paroxysmal tachycardia rather than to flutter. Vagus and ocular pressure failed to affect the auricle in this case, and these procedures did not increase the degree of block above 4:1. The patient, who weighed only 100 pounds (45.4 Kg.), received 1.8 Gm. of powdered digitalis during the first thirty-six hours after the first observation, and 0.2 Gm. daily thereafter, without any demonstrable effect except an inversion of the T wave. The records are similar to those in the three patients who had auricular tachycardia with partial block described by White.[11]

Atrioventricular Bradycardia; Retrograde Conduction and Reciprocating Rhythm.—On September 25, the pulse was found to be slow, with occasional coupled beats. Digitalis was discontinued. The total dose in sixteen days was 5 Gm.

---

11. Sprague, H. B., and White, P. D.: Heart-Block During Auricular Paroxysmal Tachycardia, M. Clin. N. Amer. **8**:1855, 1925.

The electrocardiogram taken the next morning (fig. 3) demonstrated a nodal bradycardia, the interval between single ventricular beats indicating a rate of 37 per minute. P waves, resembling the diphasic auricular complex seen during the tachycardia, occurred superimposed on, or directly after, these single beats. Coupled beats predominated, only a few single beats occurring each minute. The couples consisted of a nodal beat with the P wave falling 0.36 or 0.46 seconds after R and on or after T, and a similar Q R S complex from 0.26 to 0.42 seconds after this P wave. The briefer the R-P interval, the longer was the corresponding P-R interval.

During the afternoon (fig. 4) the mechanism was practically the same, except that in two instances the P wave, erect and notched, preceded isolated ventricular complexes by 0.12 and 0.19 seconds and the form of the reciprocal Q R S was typical of left bundle branch block in many, but not in all, of the

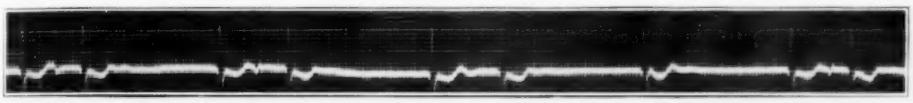

Fig. 3.—Electrocardiogram made on morning of September 26, showing atrioventricular rhythm and retrograde conduction. The P waves of most nodal beats fall on the T waves and are followed by a ventricular beat. When the P wave falls at the end of the Q R S complex, a reciprocal ventricular beat does not follow. The A-V rhythm has a rate of 37 per minute. The R-P intervals were 0.32 to 0.44 seconds.

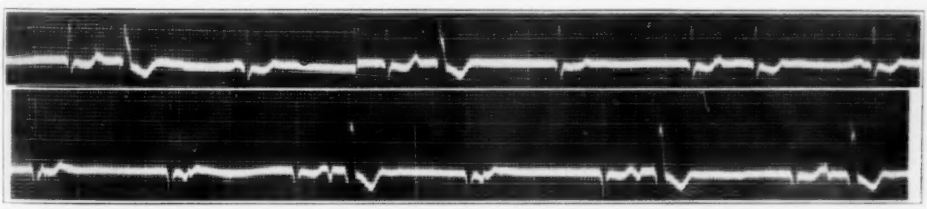

Fig. 4.—Electrocardiogram made on the afternoon of September 26. In two instances the P wave precedes the nodal Q R S. Inverted T waves are shown.

couples. When the P-R interval was 0.38 seconds or more, a normal ventricular complex followed. On September 27 (fig. 5), the nodal rhythm was still present, the rate was 60 per minute and cycles from 4 to 11 beats in length showed the P wave first preceding, then coinciding with, and later falling behind, the Q R S, and finally falling early on the T wave and provoking a reciprocal ventricular response, which occasionally approached the confiuration of the left bundle branch block. The P waves preceding the Q R S were erect but deeply notched; those which followed were diphasic. The T waves, inverted on the previous day, were now erect.

In most cases of reciprocal rhythm variations in the form of the second ventricular complex are noted, but this case seems to be unique in that it demonstrates clearly the relation of the interval between the first and second ventricular complexes to the occurrence of reciprocal beats of aberrant form. Normal ventricular complexes and bundle branch block occur in the same tracings constantly. The block occurs when the interval between the two beats is relatively short, and by measuring the length of the intervals in which block occurs and those in couples with normal intraventricular conduction, one can measure the refractory period of the left branch of the bundle. This varies from day to day. On September 26 the duration of the refractory period lay between 0.64 and 0.69 seconds; on September 27, between 0.47 and 0.55 seconds; on September 28, it was less than 0.44 seconds; on October 6, it was between 0.66 and 0.70 seconds; on October 7, it was between 0.60 and 0.68 seconds. The same relation of aberrant supraventricular complex in the second beat of a couple to the duration of interval between the two beats was noted by Scherf [12] in a case in which coupling presumably was the result of 2:1 sino-auricular block with ventricular escape. The curves that were published seem typical of reciprocal rhythm.

That the conducting system above the bifurcation of the bundle is also in a critical state is demonstrated by the relation between the R-P and P-R intervals of the coupled beats. While the sum of R-P and P-R intervals varies from day

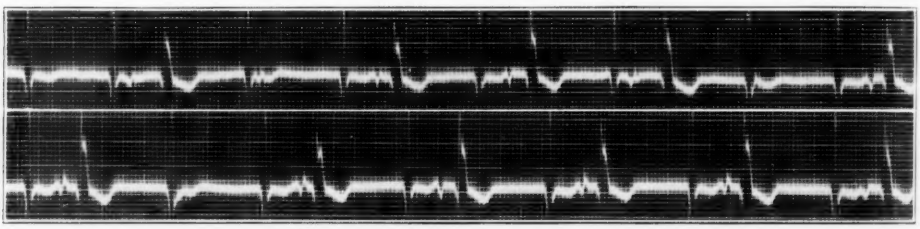

Fig. 10.—Electrocardiogram made on October 8. The upper tracing was made ten minutes and the lower thirty minutes, after the administration of atropine, 1/50 grain (1.3 mg.) subcutaneously. The nodal rate was 68 per minute.

to day, it is apparent here, as was noted by Scherf [12] experimentally, that the duration of the P-R interval varies inversely with that of the preceding R-P. That part of the conducting system below the site of origin of the nodal rhythm undoubtedly carries both the nodal and the reciprocal impulse, and the rate of conduction in this part of the path of the reciprocal beat probably varies inversely with the time consumed by the impulse going to and returning from the auricle. The double pathway postulated by Drury extends from the site of the pacemaker in the node to the auricle and back again, and it is known that retrograde conduction over this pathway may be slow and varies inversely with the rate of the nodal rhythm. It therefore seems reasonable that the fibers which are refractory to the retrograde impulse will have recovered more completely and conduct more rapidly when the R-P interval is greatest. Hence, the shortening in P-R with lengthened R-P can be a summation of effects in the portions of the path of the reciprocal impulse above and below the site of the pacemaker in the node.

12. Scherf, D., and Shookhoff, C.: Experimentelle Untersuchungen "über die" Umkehr Extrasystole, Wien. Arch. f. inn. Med. **12**:500, 1926.

SUMMARY

A case of atrioventricular rhythm is reported in which retrograde conduction and reciprocal rhythm were present, and in which left bundle branch block occurred at times in the reciprocal beat.

The first period of nodal rhythm followed twenty-two days of paroxysmal auricular tachycardia with partial heart block; it lasted four days, and the rhythm gradually reverted to normal. Nodal rhythm recurred in eight days and continued for the six days that the patient remained under observation. The effects of vagal pressure and of the administration of atropine were observed.

EXPERIMENTAL OBSTRUCTIVE JAUNDICE

II. MODIFICATION OF THE PARATHYROID TETANY MECHANISM IN JAUNDICE *

WILLIAM C. BUCHBINDER, M.D.
AND
RUTH KERN, M.S.
CHICAGO

Fairly conclusive evidence that one or more of the metabolites arising in obstructive jaundice may produce a functional or structural alteration in some part of the mechanism producing tetany is afforded by the absence or diminution in the neuromuscular response under conditions in which severe tetany would otherwise be evoked. The evidence is threefold. In the late obstructive jaundice of puppies induced by ligation and division of the common bile duct, a marked lowering of the blood serum calcium occurs, which may reach the tetany level.[1] Apart from certain intercepting factors, the early precipitation of tetany might be expected in very young animals with severe injury to the liver and disturbance in the intestinal tract. Some apathy and slight depression occur as a rule. As a further test of the foregoing hypothesis,[2] the parathyroids were removed from animals with obstructive jaundice. In a preliminary report [3] of the effect of thyroparathyroidectomy on the jaundiced animals, attention was called to the absence of manifest tetany in more than half of the puppies and the relatively long survival period of the adult animals that showed a marked diminution in the severity of the tetany. By such crucial experiments, we were able to evaluate the parathyroid factor and were led to conclude that the parathyroids had not assumed an added function or were playing some rôle in keeping the animal free from tetany, in so far as jaundiced animals on which parathyroidectomy had been performed also revealed apathy and

* From the Nelson Morris Fund and the John D. and Fannie K. Hertz Fund of the Michael Reese Hospital and the Nelson Morris Institute for Medical Research, and the Department of Physiology of the University of Chicago.

1. Buchbinder, William C., and Kern, Ruth: Blood Calcium Deficiency in Experimental Obstructive Jaundice, Am. J. Physiol. **80**:273 (April) 1927; Experimental Obstructive Jaundice: I. Growth Factor in Defective Calcification, Arch. Int. Med. **40**:900 (Dec.) 1927.

2. Buchbinder, William C., and Kern, Ruth: Blood Calcium Deficiency and Bone Changes in Experimental Obstructive Jaundice, Am. J. Physiol. **81**:468 (July) 1927.

3. Buchbinder, William C., and Kern, Ruth: The Effect of Thyroparathyroidectomy on the Jaundiced Animal, Proc. Soc. Exper. Biol. & Med. **25**:3, 1927.

muscular atony and died from what appeared to be circulatory failure. Lastly, the observation of fairly prompt relief from tetany, even though transient, is offered as a third piece of evidence.

METHOD

Fourteen adult dogs were thyroparathyroidectomized after jaundice had been induced by division of the common duct between ligatures. The duration of the jaundice ranged from one to thirty days. The same procedures were carried out on ten puppies from 8 to 10 weeks of age which comprised parts of three litters. Two additional pups, nonjaundiced litter mates, which were thyroparathyroidectomized served as controls.

Blood serum calcium determinations were made in the normal, icteric and subsequent parathyroprivic states. In the latter, they were made from every twenty-four to forty-eight hours, so that one could be reasonably assured that parathyroidectomy was complete. The Kramer-Tisdall [4] technic was employed.

During the normal and icteric states and prior to thyroparathyroidectomy, the animals were fed a stock diet. Following the latter, they were fed solely a diet of cooked meat. For dietary control purposes, a single litter of pups received a ration consisting of cooked cereal, bread and milk.

Collip's parathyroid extract [5] was administered to three animals. Only one of these exhibited tetany. It received from 20 to 100 units on the eighth, ninth and tenth days after thyroparathyroidectomy. The other two animals received 100 units on the eighth day and subsequently when they became moribund. Eleven days after thyroparathyroidectomy the excretion rate of calcium chloride from the blood stream was determined on the same two animals, following the administration of a 10 per cent aqueous solution of calcium chloride (100 mg. per kilogram).

The intravenous injection of dog's whole bile was carried out on two thyroparathyroidectomized animals exhibiting severe tetany. One of these was jaundiced, the other nonjaundiced.

RESULTS

In tabulating the data, it has been considered advisable to refer to the results obtained after thyroparathyroidectomy on three groups of jaundiced animals: the puppies, the adult dogs acutely jaundiced and the adult dogs chronically jaundiced. All of the puppies, except the two controls and most of the adult animals, were jaundiced from sixteen to eighteen days before thyroparathyroidectomy. To avoid confusion, we have referred to these animals as chronically jaundiced.

The survival period after thyroparathyroidectomy for nine chronically jaundiced adult dogs which were untreated and the sole diet of which consisted of cooked meat ranged between one and one-half and seventeen and one-half days. Six of these had a mean survival period

4. Kramer, B., and Tisdall, F. F.: A Clinical Method for the Quantitative Determinations of Calcium and Magnesium in Small Amounts of Serum and Plasma, Bull. Johns Hopkins Hosp. **32**:44 (Feb.) 1921.

5. The extract used was parathormone, furnished for the purpose of this investigation by Eli Lilly & Company.

of more than ten days. Three died within three days of the operation; one of the latter was a lactating animal. Terminal tetany in this group occurred in only two instances. Although these animals exhibited a tetany varying in intensity from the mild form in which there was regional muscle fibrillation to a most severe type, the former was much more commonly noted, and in these cases it was intermittent and transient. In all instances it was the usual rule to note its complete abatement two or three days before death in whatever type of tetany was displayed; the animal then became stuporous, lethargic and comatose (fig. 1 and table 1).

The survival period for the group of ten puppies had a mean average of 3.8 days, which is slightly longer than the expectancy for animals of this age. Three of them lived from five to eight days after thyroparathyroidectomy. Three animals exhibited a tetany which

Fig. 1.—The dog on the left (Bl.) ten days after thyroparathyroidectomy, showing marked muscular atony and depression. This animal lived more than a week after this photograph was taken. The blood calcium remained below 4 mg. after the tenth day. The dog on the right (Daph.) is shown twelve days after thyroidectomy in slight tetany.

was slight to moderately active, and in only one instance did it appear to be terminal. It was much less severe than that observed in the two nonjaundiced thyroparathyroidectomized litter mates that were used as controls. On the other hand, the complete absence of manifest tetany was noted in more than half the animals of the series. The clinical picture and the survival period were not changed in the one litter which received rations of only milk, cereal and bread.

For the group of five acutely jaundiced adult dogs (thyroparathyroidectomized twenty-four hours after division of the common duct) the survival period was a little more than two days. The tetany which developed in three of the animals was severe and terminal. One of the animals lived ten days, and never exhibited the slightest active tetany.

The Time of Appearance and Severity of the Tetany of Jaundiced Thyroparathyroidectomized Dogs and the Blood Serum Calcium*

Dogs	No. Days Jaundiced	Days After Thyroparathyroidectomy 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	No. days Lived After Thyroparathyroidectomy
ADULT DOGS																				
Snd.	16	0	0	+++ (4.6)	+++ (5.2)	+++	0	0	0	..	..	..	..	..	..	..	..	..	..	7½
Rth.	17	++ (7.0)	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1½
Sad.	17	+ (7.8)	+	0	0 (6.9)	0 (5.6)	0	0	0	0	..	..	..	..	..	..	..	..	..	8½
Daph.	18	0 (7.4)	0	+ (7.4)	0	+	0	+ (4.9)	0	+	+ (3.6)	+	+ (3.6)	+	0	..	..	..	..	13½
Snw.	18	+++ (7.7)	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1
Bl.	17	0 (8.3)	0	+	0 (4.7)	0	+	0 (4.9)	+	0 (4.4)	0	+ (3.9)	0	0	+ (3.3)	0	0	0	0	17½
Ce.	17	0 (8.2)	++++ (6.8)	++	0	+++ (5.9)	0	0 (4.3)	+	0 (3.3)	0	..	..	..	..	..	..	..	..	10
Bz.	10	+ (9.7)	0	+++ (5.8)	+	+ (5.9)	0	0	..	..	..	..	..	..	..	..	..	..	..	7
Lra †	39	0 (8.2)	0	0	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	3
Jn.	1	0 (5.8)	0 (5.8)	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2
Am.	1	0 (8.2)	0	0	0 (4.5)	0	0	0 (3.8)	0 (4.6)	0 (3.4)	0	..	..	..	..	..	..	..	..	9½
Spt.	1	0 (8.7)	+++	+++	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2½
Nel.	1	0 (8.5)	+++ (6.4)	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2
Wht.	1	0 (7.4)	+++	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2
PUPPIES																				
Tan.	17	0 (7.9)	+ (5.5)	++	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	3½
An ‡	0	++++ (8.0)	++++ (4.0)	..	..	..	Litter received ration of milk, bread, and cereal													2
Cn ‡	0	++++ (8.3)	++++ (4.9)	+	+++	++++														4½
Wf.	18	0 (3.9)	0 (4.0)	..	..	..														2
Cndl.	17	0 (4.2)	0	..	..	..														2
Bob.	18	0 (5.9)	0 (3.6)	0	..	..														2½
Er.	16	0 (6.3)	+	0	++	+	..	..	..	..	..	..	..	..	..	..	..	..	..	4¼
Sae.	16	0 (8.7)	+ (6.4)	0	0	..	..	..	..	..	..	..	..	..	..	..	..	..	..	3½
Spt.	16	0 (5.8)	0	0	0	0	0	+	+	..	..	..	..	..	..	..	..	..	..	7½
Ull.	16	0 (4.8)	0	0	0	0	0	0	0	..	..	..	..	..	..	..	..	..	..	7½
Herm.	16	0 (5.7)	0	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1½
Tip.	16	0 (7.2)	0	0	0	0	..	..	..	..	..	..	..	..	..	..	..	..	..	5

* +, very slight active tetany; ++, moderate; +++, severe.

† Lactating animal.

‡ Nonjaundiced controls.

In considering further the symptomatology of the three groups of animals additional observations may be worthy of mention. A peculiar expiratory groan associated with some slight expiratory difficulty but without hyperpnea occurred in all of the puppies. Apart from the hyperpnea occurring in the adult animals a similar respiratory difficulty was noted. The groan, however, was conspicuously absent except in a few instances. Most of the adult animals that lived more than nine or ten days developed decubital ulcers. Although anorexia was marked in several of the dogs, others maintained an appetite that was voracious nearly to the end. In all, a grade of extreme emaciation and cachexia supervened before death. Atony of the sphincters with involuntary urination and defecation occurred at the end. The animals that lived

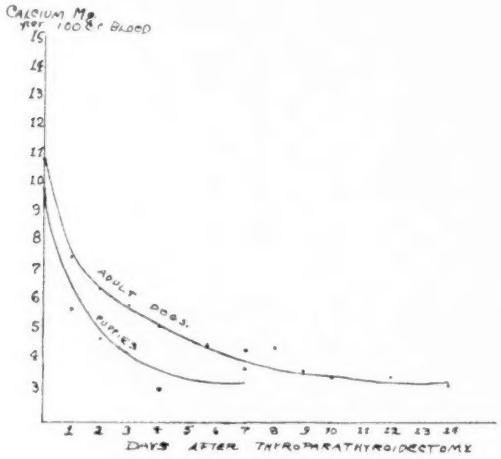

Fig. 2.—Showing the general trend of the blood calciums in jaundiced-thyroparathyroidectomized animals. Note the more acute drop for the puppy.

for a relatively short time, and especially the puppies which did not exhibit any active form of tetany, appeared to die of an acute poisoning. Retching and vomiting occurred more often in the younger set of animals. Spotting of the stools with blood, the result of an enteritis observed in the pups before thyroparathyroidectomy, was aggravated following this procedure. The adult animals, which uncommonly showed blood in the stools during their jaundiced state almost invariably developed a bloody diarrhea following thyroparathyroidectomy.

There are no significant changes in the level of the blood serum calcium for the adult animals and puppies after a period of jaundice lasting from sixteen to eighteen days. The blood serum calciums of the two groups approximate one another before and after the induction

of jaundice. Twenty-four hours after thyroparathyroidectomy, the calcium values of the puppies fall to a considerably lower level than those of the adults (fig. 2). Insufficient determinations for the subsequent days do not enable us to draw any conclusions about the trend of the blood calcium in the two respective groups, but there appears to be a more acute lowering in the puppies following thyroparathyroidectomy.

Within a few minutes after the intravenous injection of 10 per cent aqueous solution of calcium chloride the blood serum calcium approached that of the normal without the animal exhibiting any change in the picture of extreme apathy and stupor. The excretion rate extended over approximately four hours (fig. 3). The injection of Collip's parathyroid extract on the same dogs three days before the injection of calcium chloride was carried out revealed the inefficacy of this hormone extract to raise the blood calcium level in the para-

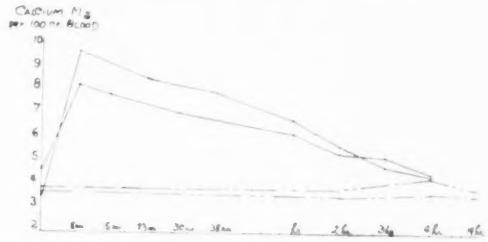

Fig. 3.—Showing the curve of excretion of calcium chloride and the inefficacy of Collip's parathyroid extract in materially affecting the blood serum calcium in jaundiced-thyroparathyroidectomized dogs. The continuous line indicates the excretion of calcium chloride from the blood after intravenous administration of 0.0100 gm. per kilogram (10 per cent aqueous solution). The broken line indicates the curve following the administration of 50 units of Collip's parathyroid extract.

thyroidectomized jaundiced animal. It did not produce any change in the symptoms at this time, nor did it seem to delay death when the animals became moribund, although it may have hastened it in one instance. It was administered to a third animal on the eighth, ninth, and tenth days in doses of from 20 to 100 units, but a progressive lowering of the blood calcium of from 5.0 to 4.2 mg. per hundred cubic centimeters of blood occurred until near death, when it rose to 5.7. The tetany in this animal, though not controlled, became less severe, and the terminal picture of extreme stupor was identical with that of the other untreated animals.

The intravenous injection of whole bile into two parathyroidectomized dogs, one jaundiced, the other nonjaundiced, was followed by

a relief from the symptoms of tetany. The nonjaundiced animal received 2 cc. (injection rate was 1 cc. per minute) on the third day after thyroparathyroidectomy when it exhibited marked depression and severe tetany. Two minutes after the injection, the picture changed completely, the animal becoming lively and appearing a little excited; the tetany was completely abolished. Relief from the latter, however, was only transient, and thirty minutes after the injection, the animal developed a seizure. It died the next day of tetany. The jaundiced animal received 12 cc. of bile four days after thyroparathyroidectomy. Ten minutes after the injection, it was relieved of tetany, which did not reappear. It died the following day, apparently from an overdosage.

COMMENT

While most of the experimental data already accumulated on the pathogenesis of tetany suggests that either a low concentration of calcium or the action of toxins is responsible for the onset of tetany, the production of an experimental animal with low blood calcium and a toxemia without manifest symptoms of tetany calls for comment. Unless one or more of the metabolites arising in obstructive jaundice may directly or indirectly alter the mechanism of tetany in susceptible animals so as to prevent the appearance of tetany, neither of the current views is adequate to explain the results of these experiments.

For the adherents of the toxin theory of tetany the question is especially pertinent as to why a more acutely fatal outcome does not follow parathyroidectomy at a time when extensive morphologic changes in the liver and injury to the gut have already been wrought, especially when these are superimposed on the already existing toxemia of jaundice. It has been suggested by several investigators that in the parathyroidectomized dog that has adjusted itself to an amenable existence without developing tetany the liver may have taken over the function of the parathyroid glands.[6] A different opinion has been expressed by Blumenstock and Ickstadt,[7] who believe that the liver plays the essential rôle in the development of the so-called toxemia of parathyroidectomized dogs. They found that parathyroidectomy in animals in which an Eck fistula had been produced resulted in a delay in the appearance and a diminution of the severity of the characteristic symptoms. Since the syndrome of tetany may be so modified and made less severe under conditions in which there are underlying morphologic changes in or a perversion of function of the liver, it may be postulated

6. Dragstedt, L. R.; Phillips, K., and Sudan, A. C.: Studies on the Pathogenesis of Tetany: II. Mechanism Involved in Recovery from Parathyroid Tetany, Am. J. Physiol. **65**:368 (July) 1923.

7. Blumenstock, J., and Ickstadt, A.: A Note on the Role of the Liver in Parathyroid Tetany, J. Biol. C. **61**:91 (Aug.) 1924.

that this organ may ordinarily, through its unrestricted activity, produce the substances which give rise to the typical syndrome of tetany. In a preliminary report we called attention to some similarity in the symptoms of their animals and those of ours, and, with the evidence obtained from these experiments, we would subscribe to such a view and suggest further that the same products arising from the perversion of liver function in the Eck fistula and in the jaundiced animal may play an active rôle in intercepting the usual nervous phenomena. While parathyroidectomy in a jaundiced animal produces an overwhelming toxemia, the animal lingers, becomes stuporous and dies of what appears to be cardiac failure. The extension of life certainly does not occur by virtue of the insult added to the injury already done, but is probably the result of an ineffectual nervous mechanism which would otherwise abruptly terminate life. In jaundice, the nervous mechanism seems to be protected not only against toxins arising as the end-products of intestinal putrefaction, but also against the extremely low concentration of the blood serum calcium. Calcium administered to such an animal is ineffectual in changing the symptomatology of those which were in a state of severe depression. The excretion rate of calcium chloride from the blood of these animals, however, shows a response that is more nearly comparable to that of a normal animal rather than that described for one jaundiced alone.[8] The cause for this relative loss of calcium-fixing powers which have been ascribed to icteric blood is a matter of surmise apart from its being one of a number of failing physiologic mechanisms. Also the inefficacy of the parathyroid hormone extract in materially affecting the blood serum calcium may be analogous to the failure of response of other gland preparations after their administration under certain conditions.[9]

There has been almost unanimity of opinion that bile acts as a depressant on the central nervous system. Meltzer and Salant [10] concluded that bile contains a tetanic element or an agent which causes increase of excitability of the nervous system as well as depressive elements, and that the two are antagonists. The experiments of Lyon-Caen [11] led him to conclude that bile and biliary salts retard muscle

8. Walters, W., and Bowler, J. P.: Pre-operative Preparation of Patients with Obstructive Jaundice: An Experimental Study of the Toxicity of Intravenous Calcium Chloride Used in the Preparation of Patients, Surg. Gynec. Obst. **39**:200 (Aug.) 1924.

9. Strouse, S., and Schultz, O. T.: Insulin in Diabetes Complicated by Infection, J. A. M. A. **80**:1592 (June) 1923.

10. Meltzer, S. J., and Salant, William: Studies on the Toxicity of Bile: II. The Toxic Effects of Bile Upon the Central Nervous System and the Elimination of Strychine Through the Bile in Nephrectomized Animal, J. Exper. Med. **8**:127 (Jan.) 1906.

11. Lyon-Caen, L.: Action de la bile et des sels biliares sur l'excitabilite neuromusculaire, Compt. rend. Soc. de biol. **93**:237 (June) 1925.

chronaxia while nerve chronaxia remains unchanged. Our own observations indicate that the immunity of the neuromuscular mechanism is more evident when the jaundice is of some duration. In most instances, the acutely jaundiced animal develops a rapid and severe terminal tetany. While up to the present attention has been directed to the striking way in which the effects of jaundice may alter the typical syndrome that follows thyroparathyroidectomy, a consideration as to how the latter may affect the jaundiced state must not be omitted.

In view of the fact that the symptom-complex following parathyroidectomy of the jaundiced animal is parallel in so many ways to that which would accrue in the icteric animals which were allowed to die of a terminal cholemia, parathyroidectomy might be looked on as a hastening process. The listlessness, languor, stupor and coma that supervene before death are alike in both conditions. We must therefore consider that parathyroid failure may enter as a cause of death in the jaundiced animal, especially in the young one which may live well over 100 days after ligation of the common duct and in which a progressive lowering of the blood serum calcium to low levels occurs, but that tetany does not occur because of some compensating mechanism that develops with chronicity, as suggested by Prof. A. J. Carlson. When the very young animal is parathyroidectomized only twenty days after ligation of the common duct, glands more physiologically active are removed, hence the slight or masked symptoms of tetany and the relatively premature death. Such a theory of parathyroid failure seems less applicable for the adult animal, in which normally constant calcium values obtain throughout the course of obstructive jaundice. But the survival period of the puppy after ligation of the common duct is much longer than that for the adult animal, and the marked lowering of the blood serum calcium in the former occurs only late in the obstructive jaundice, at a time when the adult animal would long since have been dead.

The relief of symptoms of tetany following the intravenous injection of bile is of interest, but further experimentation with the biliary constituents will have to be carried out before its bearing on the absence of tetany in jaundice is ascertained. The action of circulating bile may be similar to that of peptone, which Carlson [12] has noted produces a temporary suppression of tetany and for which some depression of the nervous tissues was suggested as the probable mechanism. It is possible, too, that bile produces its effects through a change in the p_H of the blood.

12. Carlson, A. J., and Jacobson, Clara: Further Studies on the Nature of Parathyroid Tetany, Am. J. Physiol. **28:** 133 (June) 1911.

SUMMARY AND CONCLUSIONS

1. There is a marked diminution generally or an absence of tetany following thyroparathyroidectomy on jaundiced adult dogs and puppies.

2. The survival period after thyroparathyroidectomy is prolonged, especially for animals that have been jaundiced for some time.

3. The acutely jaundiced dog is more susceptible to a severe and terminal tetany.

4. Indirect evidence is presented of a functionally or structurally altered mechanism of tetany in obstructive jaundice. This is threefold and is based on: (a) the response of the thyroparathyroidectomized animal; (b) the relief of tetany by the intravenous injection of bile, and (c) the absence of tetany in late obstructive jaundice in puppies in which the blood serum calcium may reach the tetany level.

5. It is thought that the threshold of nervous excitability is raised in obstructive jaundice. This is in harmony with the belief that bile acts as a depressant for the central nervous system, concerning which there has been almost unanimity of opinion.

Book Reviews

THE HARVEY LECTURES, 1925-1926. SERIES XXI. Price, $4. Pp. 229, with illustrations. Baltimore: Williams & Wilkins Company, 1927.

The present series of the Harvey Society Lectures is fully up to the usual standard, consisting as it does of reviews on anatomy, histology, physiology, biochemistry and physicochemistry, mathematics, and medical history by authorities representing more or less equally American and European schools.

F. R. Nager of Zürich, the first otologist to deliver a Harvey Lecture, emphasizes the importance of histologic work in diseases of the ear, especially those of the middle ear, in regard to tuberculosis, malignancy, cholesteatoma, otosclerosis and experimental noise-deafness. In the last, air conduction is to blame for the degenerative changes in the organ of Corti. The histology of the labyrinth is difficult to study in man because of early postmortem changes, but the available work is reviewed.

The lecture by J. H. Northrop of the Rockefeller Institute on the "Dynamics of Pepsin and Trypsin" seems to have dispelled definitely another mystery of so-called colloid chemistry as regards the explanation of enzyme action. In a series of beautiful, critical experiments in which changes in the viscosity or conductivity of a solution were used as a measure of the rate of reaction of enzymes, an inverse linear relationship was found between the time it took for a small change in viscosity and the concentration of the pure enzyme. The law of mass action was found to hold quantitatively for action of the "inhibitors" —peptone, plasma—so that one could assume that

$$\frac{[\text{free trypsin}]\,[\text{free inhibitor}]}{[\text{trypsin-inhibitor}]} = \text{a constant}$$

The agreement between observed values and those calculated from the equation was proved in a series of experiments arranged to control separately the concentration of enzyme and inhibitor.

The study of the spontaneous deterioration or inactivation of the enzymes demonstrated again the correspondence with the mass law, if one took into account the "free," that is, uncombined with inhibitor, active enzyme. The combined form is stable but dissociates into the active enzyme on dilution, just as the salt of a weak acid and base undergoes hydrolysis.

The kinetics of trypsin is extremely complicated, but Northrop could show agreement with monomolecular time-curves under proper experimental conditions. Thus the velocity of digestion of casein by trypsin at any time depended solely on the concentration of the active enzyme at that time. Much evidence is adduced against the catalytic theory, and equations are derived to explain why Schütz's rule holds within a certain range only.

The close relationship between the titration curves of proteins and their rate of digestion and the influence of p_H, point to the conclusion that only the protein anion is attacked by trypsin, the cation by pepsin. Trypsin itself behaves exactly like a monovalent cation in a Donnan-ratio experiment from p_H 2 to 10.2, beyond that as an anion; pepsin behaves as an anion below p_H 6. No compound is formed between the enzyme and the protein. The enzyme is completely ionized. Hence enzymes behave exactly as many other simpler chemical substances, and the complex nature of their reactions is due entirely to the fact that several reactions occur simultaneously—a fact not sufficiently appreciated nor properly controlled until this work by Northrop.

In the next lecture, W. H. Lewis of the Carnegie Institution of Washington, discusses the transformation of mononuclear blood cells into macrophages, epithelioid and giant cells, bringing forward strong evidence in support of the

monistic view. The vitally stained hanging drop of whole blood—blood cultures on a cover slip—and spreads of living tissue were the methods used. The work is entirely convincing to the reviewer; so also is that of Sabin, Carrel and Maximow whose views are energetically disputed by Lewis. When such authorities disagree on fundamental grounds, interesting work may be expected in the future.

J. B. Collip of the University of Alberta gives an excellent review of the anatomy, physiology and pathology of the parathyroid glands including a discussion of clinical forms of tetany. He then presents his own brilliant researches culminating in the extraction, isolelectric purification and standardization of the parathyroid hormone, whose specific action consists in elevating the level of blood calcium in normal or parathyroidectomized animals and patients. Tetany may thus be abolished by appropriate parenteral administration of the extract. On the other hand, hypercalcemia—20 mg. or more per hundred cubic centimeters—may be produced, leading to a characteristic syndrome with terminal failure of renal function, marked nitrogenous retention, hyperphosphatemia and acidosis. The blood becomes extremely viscous, and hemorrhages of the mucous membrane are constantly found in the gastro-intestinal tract. Rabbits and rats are resistant to the hormone. Calcium lactate by mouth enhances the action of the hormone reducing the amount necessary in human cases. Satisfactory results have been obtained in clinical hypoparathyroidism. After Collip's work, the guanidine theory of parathyroid tetany has scarcely a leg on which to stand.

"Empiricism and Rationalism" are presented by E. B. Wilson of Harvard University in a keen, illuminating style. Statistical analysis is shown to be essentially descriptive or empirical as contrasted with the experimental method or rationalism. "The place for complicated mathematics is in the follow-up." It is not of much use in the original discovery. The value of mathematics to the scientist is not to teach him formulas, but how to formulate. Wilson points out clearly the limitations of statistical equations, the adjustability of their constants as compared with the fixed constants in some natural laws, and the uselessness of looking for correlations by the statistical method if antecedent rationalism has not been employed. The exact sciences make little use of statistics because good control is available. A plea is made in the case of the beginner in science for qualitative experiments and for a return to the "stubborn facts of nature" instead of juggling with complicated mathematics or highly intricate apparatus.

A scholarly review of the development of modern therapy beginning with the application of the statistical method by Louis in the early nineteenth century to the effects of venesection on various acute diseases, is presented by Knud Faber of Copenhagen who contrasts the Renaissance of clinical entities by Laennec and Bretonneaus with the development of experimental pharmacology by Magendie, who led up to the German physiologic school of medicine. The latter fell short of ideal therapy because it treated the disturbed function and not the specific disease. In the last quarter of the nineteenth century and in the first quarter of the twentieth century the principle of clinical entities has become firmly established through the discovery of the diseases of the ductless glands and those due to specific bacterial invasion. The influence on therapeutics is too obvious to mention, but one must still distinguish between symptomatic therapy and curative therapy. The latter is obtainable only after the disease can be reproduced experimentally.

B. Brouwer of Armsterdam gives the last lecture, dealing with the correlation between comparative anatomy and neuropathology. Striking evidence is brought forward for the division of the cerebellum into the "neo" and "paleo"-parts, the latter consisting of the vermis, flocculus and paraflocculus. The neocerebellum is less resistant to injurious agencies. The olivary system can also be shown to consist of "neo"- and "palco"-divisions. The origin of the midline oculomotor nucleus of Perlia is connected with the frontal position

of the eyes and the overlapping of the visual fields, and its close special relationship to the Westphal-Edinger nucleus for pupillary contraction is given as an example of neurobiotaxis. The columns of Goll and Burdach develop phylogenetically with the gnostic or "neo" sensibility as distinguished from "paleo" or vital sensibility, represented chiefly in the gray matter of the posterior horn. The trigeminal nerve has "neo"- and "paleo"- nuclei autonomic functions which belong to the "paleo" system, and are represented by much more complex tracts than the "neo" system. The visual tract extending from the external geniculate body to the occipital cortex is an example of the superimposition of the new system on the old reflex visual pathways to the midbrain, occurring presumably to allow exact visual localization by the higher forms of animal life.

MODERN MEDICINE: ITS THEORY AND PRACTICE. Volumes 4 and 5. Edited by SIR WILLIAM OSLER, BART, M.D., F.R. S. Reedited by THOMAS MCCRAE, M.D., assisted by ELMER H. FUNK, M.D. Third edition, thoroughly revised. Price, $9 per volume. Philadelphia: Lea & Febiger, 1927.

In volume 4, diseases of the respiratory and circulatory systems are discussed, and in it the high standard of the previous volumes of this series is maintained. While this edition loses none of the charm associated with the list of notable contributors of the original edition, it has been effectively brought up to date. It contains chapters written by Morris, Christian, Hoover, Herrick, Babcock, Howard, Gibson, Osler, Lewis, Maude Abbott and others well known in medical literature. Each chapter covers the subject thoroughly, the whole being a complete general treatise of the diseases of the respiratory and circulatory systems. The chapter on the "Rate and Mechanism of the Heart Beat" by Sir Thomas Lewis is a presentation of electrocardiography stated in simple terms and without undue emphasis on the clinical value of this observed phenomenon and in such terms that the general practitioner can readily grasp it. The chapter on "Congenital Cardiac Disease" by Maude E. Abbott is, in fact, a marvelous and authoritative monograph of this whole field, occupying 200 pages of the present volume, profusely illustrated by photographs of pathologic specimens and diagrams painstakingly gathered together not only by the author but by her colleagues and predecessors at McGill; many of the specimens were collected by Osler himself.

Volume 5 covers diseases of the blood, lymphatic system, ductless glands, kidneys, and vasomotor and trophic disorders by such authorities on these subjects as Richard C. Cabot, Krumbhaar, Warthin, Longcope, Dock, John and Thomas McCrae, Rowntree, O'Hare, Hugh Young, Osler and others. Each chapter is complete and revised to date. A critical survey of the volume impresses one with the thoroughness with which each subject is covered. There is little to criticize. Especially impressive is the rational manner in which the subject of diseases of the ductless glands by George Dock, H. Lisser and Warthin is handled. They are careful and conservative in all statements, yet comprehensive and inclusive of all real advance in this field. The introduction to the diseases of the kidneys by the late John McCrae, revised by Leonard G. Rowntree, covers the recent advances that have been made in experimental medicine which may be applied to clinical medicine. Physicians are gradually establishing a rational conception of the mechanism of the function of the kidney which is of inestimable value when applied at the bedside, notably in the application of therapeutic measures. From this point of view alone the whole part devoted to diseases of the urinary system is well worth studying, especially by those who may not be familiar with recent progress made in the field of physiology of the kidneys and who are unfamiliar with the improvements in therapy as applied to the treatment in nephritis and in the nephroses.

Osler's "Modern Medicine" as represented by the present edition and as a standard system of medicine should find its place on the shelves of every medical library.

SKLEROSE UND HYPERTONIE DER INNERVIERTEN ARTERIEN. By GUSTAV RICKER. Price, 10.50 R. M. Pp. 193. Berlin: Julius Springer, 1927.

In this monograph, Ricker, who is well known for his excellent experiments on the innervation of the blood vessels, discusses in detail his conception of arteriosclerosis and hypertension. Most intensive nervous stimulation cases paresis of the constrictors of the media and stasis in the vessels of the adventitia. Compressed by the blood pressure inside of the vessels, the media is deprived of the nourishing tissue fluids and becomes necrotic. This is followed by sequestration and calcification. Less intensive stimulation leads first to an accumulation of the tissue fluids in the intima, loosening of the intima and hyperplasia of the connective tissue. Weak stimulation, finally results in constriction, narrowing of the lumen and hyperplasia of the media. One condition to which Ricker attributes much importance is the so-called peristasis. Stimulation of medium intensity produces an identical reaction of arteries and capillaries. Stimulation of the dilators leads to fluxion and hyperemia, that of the constrictors to ischemia and anemia. More intensive stimulation reveals the capillaries as the most sensitive part of the circulatory system in that their irritability disappears. At the same time the arterioles and small arteries constrict; thus, the blood passes through narrow arterioles into the wide bed of the capillaries. It flows slowly or even stagnates. These changes are of fundamental importance in many pathologic conditions, especially in nephritis, primary contracted kidney and cerebral hemorrhages.

In his antagonism to Virchow's cellular pathology, Ricker has often been attacked by those who adhere to Virchow's doctrines. Every modern clinician will read this book with much interest. It contains a wealth of thought. There is only one objection, namely, the complicated construction of sentences which Ricker uses and which makes reading difficult even for one familiar with the German language.

HYPOTENSION. By ALFRED FRIEDLANDER, Professor of Medicine, College of Medicine, University of Cincinnati. Price, $2.50. Pp. 193. Baltimore: Williams & Wilkins Company.

The author has collected a large amount of useful data on this subject and arranged them so that the reader can obtain a clear insight into the present status of hypotension. He has systematically outlined the conditions and diseases in which hypotension occurs. The temporary hypotension observed in surgical shock is duly considered, and the relation of this hypotension to decreased blood volume is discussed. Dehydration in cholera is considered the cause of the decreased blood volume and hypotension. Postural hypotension, on the other hand, is attributed to a disturbance of the vasomotor system.

The author presents in detail the different views regarding the relation of the suprarenals to blood pressure. He accepts the evidence that the suprarenal cortex is the necessary portion of the gland for maintaining normal blood pressure. Addison's disease is considered the most clearly defined clinical example of chronic hypotension. He discusses the lack of uniform benefit following specific glandular therapy in Addison's disease and emphasizes the need for further investigation of the function of the suprarenals before satisfactory therapy can be instituted. The author has not been satisfied merely to compile the known data, but he has examined them critically and has left the stamp of his own interpretation on many of them. The cleancut distinction which he makes between temporary and chronic hypotension is important from the aspects of future experimental and clinical work.

PIONEER MEDICINE IN WESTERN PENNSYLVANIA. By THEODORE DILLER. Price, $3. New York: Paul B. Hoeber, 1927.

This book is a compilation of brief bibliographies of men who, as the title indicates, were prominent in medicine during the early days in western Pennsylvania. To the reviewer the most interesting part of the entire work

is a quotation from the notes of Joseph Doddridge, written in 1824, edited under the direction of Alfred Williams and published by Joel Mensell in 1896. From the extracts of the notes it is evident that Doddridge was a keen observer and possessed considerable dramatic ability in presentation of his material.

The story of these pioneers in western Pennsylvania should be particularly interesting to readers in this locality and to all students of American medical history.

THE NORMAL DIET. By W. D. SANSUM, M.D. Price, $1.50. Pp. 136. St. Louis: C. V. Mosby Company, 1927.

The normal diet, discussed in terms that patients can well understand, is described and illustrated by menus. Chapters are devoted to the bulk requirements of the body, the acid ash type of acidosis, the acetone type of acidosis, the caloric, the protein, the mineral, the vitamin and the water requirements of the body. The author believes that the acid ash foods bear a relation to high blood pressure. He states that in a series of fifty cases, there was a drop of from 40 to 50 points in 90 per cent, after the patients were put on the proper "basic" diet. Blood pressure usually has a considerable fluctuation, and it would be interesting to follow a similar number of cases over the same period of time in which treatment was not given.

MEDIZINISCHE PRAXIS — SAMMLUNG FÜR ARZTLICHE FORTBILDUNG. Volume II — Die Magengeschwürskrankheit — Pathologie und Therapie vom Standpunkt des Internisten. Von Priv. Doz. Dr. Harald Öhnell, Krankenhaus Sabbatsberg, Stockholm. Price, 5 R. M. Leipzig: Theodor Steinkopff, 1927.

This is a seventy-five page illustrated monograph in which the etiology, pathology, symptoms, diagnosis and treatment of gastric and duodenal ulcer are briefly considered. Its purpose is to present a practical discussion of the subject in a form sufficiently concise for the use of the general practitioner. It does this extremely well.